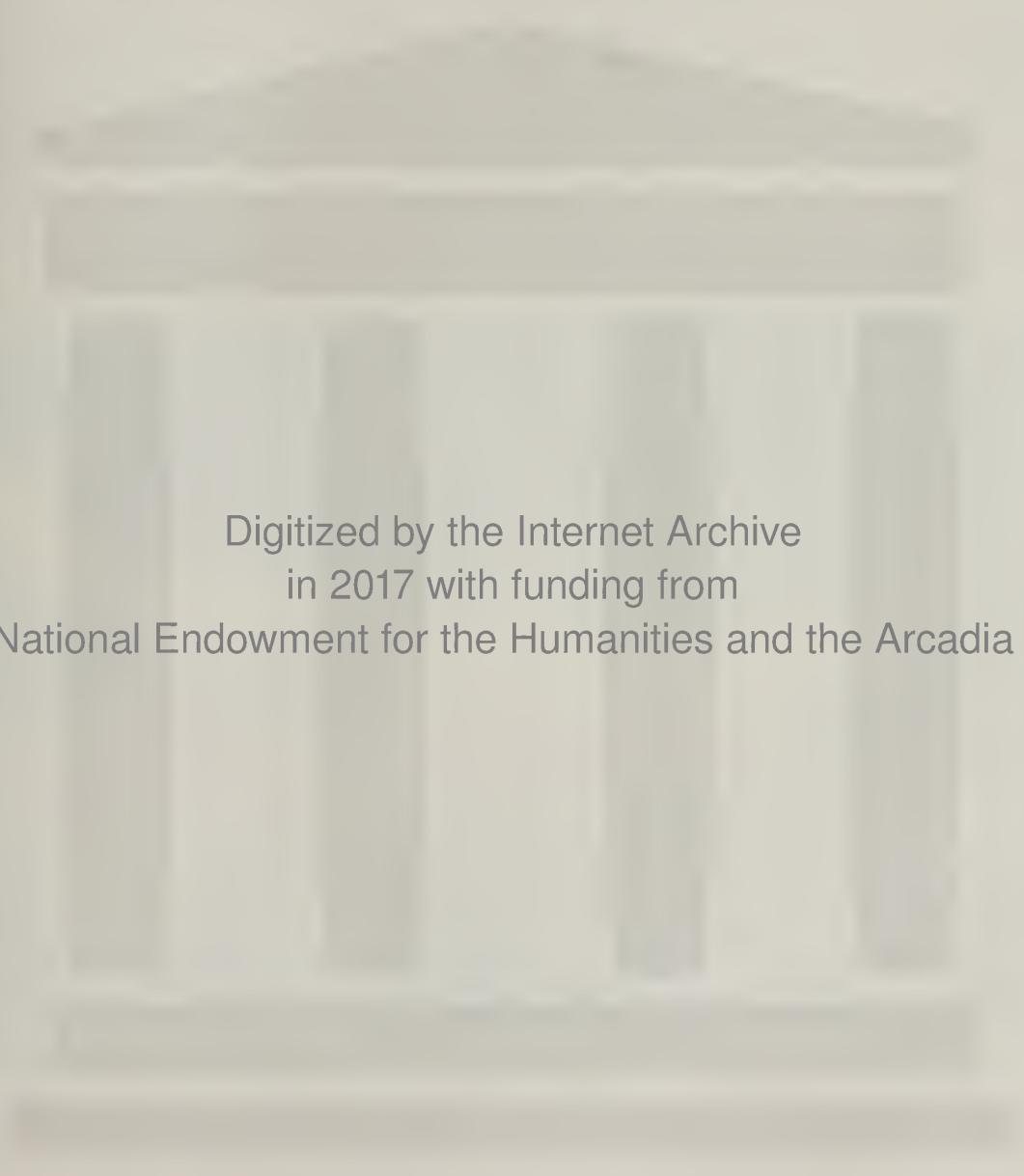


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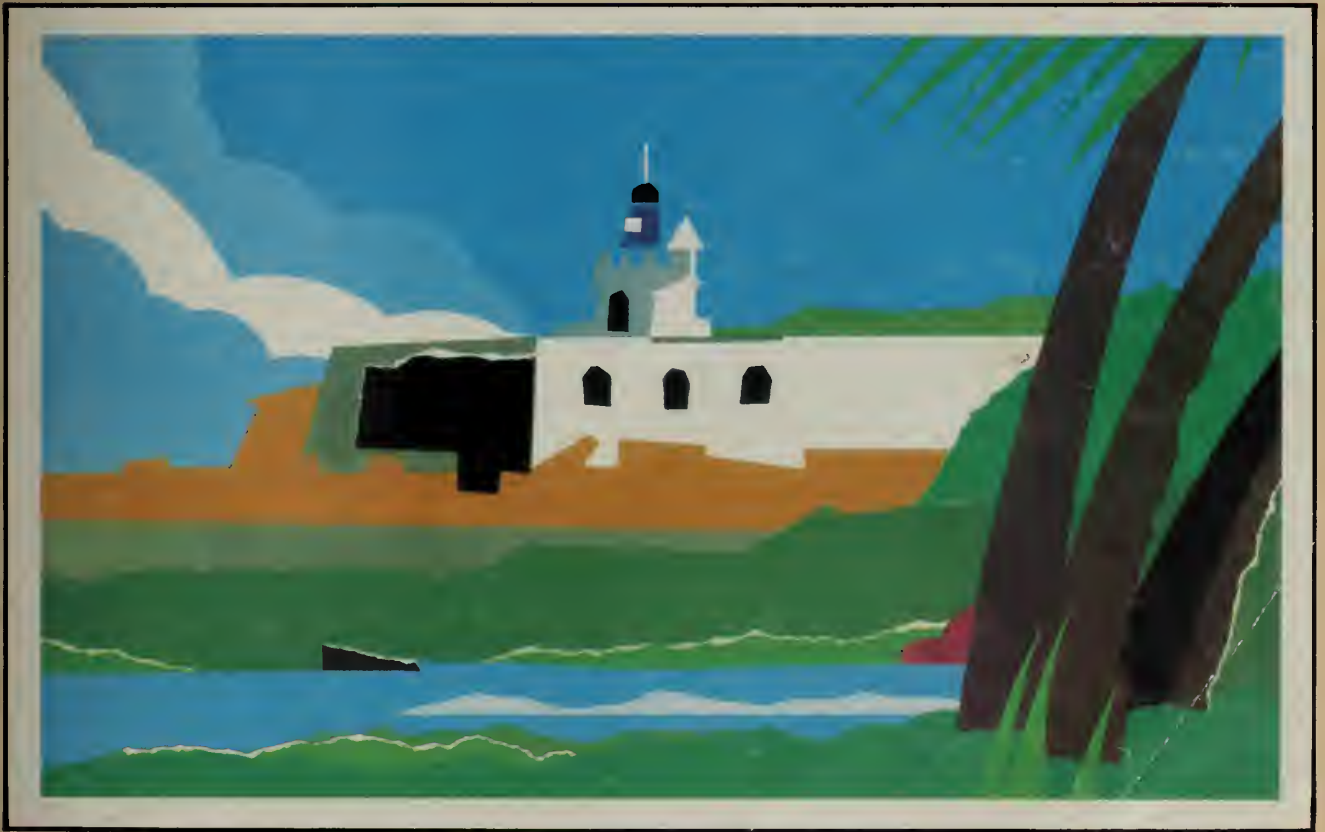
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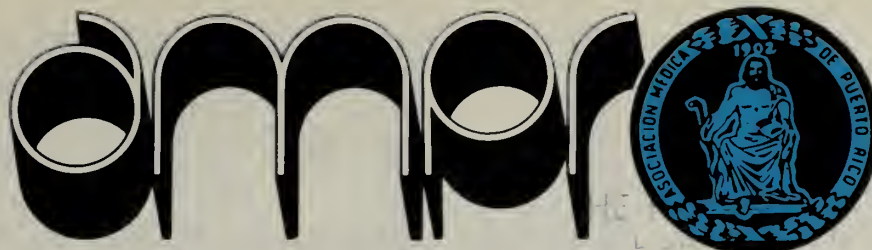
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BOLETIN

VOL.80 - NUM. 7

JULIO 1988

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Apartado 9387, Santurce, P.R. 00908

Publicación mensual, \$40.00 anuales. El Boletín se distribuye a todos los miembros de la Asociación Médica de Puerto Rico como parte de su cuota anual.

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Boletín de la Asociación Médica de Puerto Rico is published monthly for \$40.00 per year by Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, Santurce, P.R. 00908.

"POSTMASTER" Send address changes to Boletín Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, Santurce, P.R. 00908.

Second Class postage paid at San Juan, P.R.

USPS-060000

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NUESTRA PORTADA

Castillo de San Felipe del Morro, majestuoso baluarte defensivo de San Juan, visto desde el pequeño castillo del Cañuelo, al lado opuesto de la entrada del puerto, quienes han compartido la defensa de la bahía de San Juan por los últimos cuatro siglos. Debido a los frecuentes ataques a la ciudad por las flotas de las potencias extranjeras de la época: Inglaterra, Holanda y Francia, así como corsarios de todas nacionalidades, fueron autorizadas en 1539 las obras para fortificar la ciudad. El famoso ingeniero militar Juan Bautista Antonelli diseñó la estructura y el Capitán Pedro de Salazar y cuatrocientos hombres fueron los autores de la obra. La morfología, volumétrica y estética del fuerte tiene sus raíces en los castillos de Flandes. Los patios interiores, la presencia de arcos, galerías y rampas lo relacionan con los castillos europeos de la época. Sin embargo existen algunos elementos en el castillo como espacios abiertos, verandas y pórticos que señalan la presencia del ambientalismo criollo.

El castillo de San Felipe del Morro ha sido desde su creación tema para artistas puertorriqueños, españoles y norteamericanos. Estos van desde los primeros años de nuestras artes plásticas con José Campeche hasta el presente con Luis Muñoz-Lee; Isabel Bernal; Alejandro Sánchez-Felipe y Guillermo Sureda entre otros.

El Morro se ha convertido en símbolo de lo puertorriqueño, de aquí que los Institutos Nacionales de Salud lo hayan escogido como tema en el cartel que aparece en nuestra portada. En este cartel se anuncia la celebración en nuestro país del Segundo Simposio de SIDA para Profesionales de la Salud. Dicha actividad a celebrarse en el mes de agosto está además co-auspiciada por el Recinto de Ciencias Médicas de la Universidad de Puerto Rico, el Departamento de Salud de Puerto Rico y la Comisión Puertorriqueña para la celebración del Quinto Centenario del Descubrimiento de América y Puerto Rico. El arte utilizado en el cartel fue creación de Penelope Murphy y diseñado por el artista Michael Davis-Brown.

La Junta Editora del Boletín agradece a los Institutos Nacionales de Salud y a los profesores Daisy Gely y Eddie Aguilú del Decanato de Asuntos Académicos del Recinto de Ciencias Médicas de la Universidad de Puerto Rico toda su colaboración para lograr publicar este interesante cartel en nuestra portada.

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ESTUDIOS CLINICOS

Mielomeningoceles en Puerto Rico

Ricardo H. Brau, MD, FACS
Rafael Rodríguez, BS
Mayra Vera Ramírez, BS, MPH
Rosario González, MD
Virginia Martínez, MPH

El manejo del neonato afectado con mielomeningocele ha estado envuelto en grandes controversias.¹⁻¹⁹ Uno de los argumentos más criticados ha sido la selección de cual de estos niños debe ser tratado quirúrgicamente. Este dilema envuelve parámetros médicos, legales, éticos, morales, económicos, sociales y humanitarios. En nuestra institución esta controversia se ha resuelto ofreciendo servicios médicos y quirúrgicos a todos los pacientes afectados con mielomeningocele. Habiendo solucionado esta controversia nuestro mayor énfasis se concentra en buscar la mejor solución de los problemas neuroquirúrgicos que permean a esta condición. Durante el período de neonatal la mayoría de los problemas que atraviesan estos niños con mielomeningocele son de la incumbencia del neurocirujano. Algunas de las preguntas que surgen son: cuál es el tiempo óptimo para el cerrado del defecto de mielomeningocele, cuál es la mejor técnica quirúrgica, cómo hacer más efectivo el tratamiento de ventriculitis, cómo mejorar el tratamiento de hidrocefalia y cuál es el tiempo óptimo en que se debe practicar la cirugía de derivación ventricular.

Una de las variables más críticas en el manejo de estos pacientes es determinar la edad más adecuada en que se debe de reparar el defecto del mielomeningocele. El mayor argumento para la reparación del mielomeningocele ha sido la prevención de infecciones en el sistema nervioso central (SNC), aumentar la sobrevivencia de estos niños y la prevención de deterioro de la función neurológica de la placa neural.^{2, 4, 7, 8, 9, 12, 14, 16-23} Se recomienda que el cierre del mielomeningocele debe ser hecho dentro de las primeras 48 horas de nacido de acuerdo con algunas publicaciones.^{7, 8, 9, 17, 24, 25} Sin embargo, otros reportes nos indican que el cierre se puede llevar a cabo luego de las primeras 48 horas de vida sin efectos detrimentales al niño afectado con mielomeningocele.^{1, 4, 6, 18, 19, 20}

Solo hay un puñado de estudios publicados que discuten la incidencia de infecciones en recién nacidos afectados con mielomeningocele^{18, 26} y los factores de riesgo asociados a esta.

Durante la hospitalización inicial muchos de los

pacientes con mielomeningocele desarrollan síntomas relacionados con hidrocefalia.^{1, 2, 5, 9, 11, 12, 15, 18, 21-23, 27-30} El niño hidrocefálico requiere la inserción de un sistema de derivación ventricular para el control de esta condición. La complicación más seria del procedimiento de derivación ventricular es el desarrollo de ventriculitis.²⁶

Aunque la literatura médica contiene muchos reportes científicos sobre pronóstico a largo plazo de los niños afectados con mielomeningocele^{1, 6, 15-17, 24, 25, 29, 31} hay muy pocos estudios que analizan en detalle los parámetros presentes y los resultados inmediatos del neonato afectado con mielomeningocele, específicamente durante la hospitalización inicial.^{4, 18, 28}

Con estas ideas en mente decidimos recopilar nuestra experiencia y resultados en el manejo de los neonatos afectados con mielomeningocele durante la hospitalización inicial de estos. La gran mayoría de los niños nacidos con mielomeningocele en la isla de Puerto Rico y en las Islas Vírgenes Americanas son referidos para su manejo médico al Hospital Pediátrico Universitario del Centro Médico de Puerto Rico.

Materiales y Métodos

Se revisaron retrospectivamente los expedientes médicos de 128 niños tratados con mielomeningocele en el Hospital Pediátrico Universitario del Centro Médico de Puerto Rico durante enero de 1980 a julio de 1985.

Los expedientes médicos de estos 128 pacientes con mielomeningocele fueron revisados y analizados para parámetros previamente definidos (ver tabla número 1). La función neurológica de la placa neural desde el punto de vista pre y post operatorio no pudo ser evaluada adecuadamente debido a la falta de información al respecto.

Estos niños son manejados siguiendo un protocolo estándar. La mayoría de estos niños nacen fuera de nuestra institución y son transferidos al Hospital Pediátrico Universitario donde son transportados por ambulancia una vez han sido estabilizados. Son admitidos al servicio Neonatal Pediátrico, ya sea a la unidad regular o a la unidad de cuidado intensivo dependiendo de la condición general del niño. Estos niños se mantienen en posición prona, el defecto del mielomeningocele es cubierto con gasas humedecidas con solución salina. La profilaxis de antibióticos no es usada mientras se está estabilizado al

Tabla 1

Parámetro	Valores
Sexo	Varones 62 (48.4%) Hembras 66 (51.5%)
Peso al nacer	6.57 Lbs (dev st. 1.43)
Localización de la lesión	Torácica 3 (2.3%) Toraco-lumbar 41 (32.0%) Lumbar 28 (21.9%) Lumbo-sacral 56 (43.8%)
Tamaño de la lesión (N=50)	29.91 cm cuadrados
Escape de líquido	12 casos (9.4%)
Cefalorraquídeo antes de la cirugía de reparación	
Circunferencia de cabeza al nacer	36.1 cm (dev st. 4.9)
Circunferencia de cabeza antes de derivación	39.41 cm (dev st. 4.5)
Pacientes con hidrocefalia	97 (75.6%)
Edad promedio en la cual se reparó el defecto de mielomeningocele	6.6 días (dev st. 7.3)
Duración de la reparación del mielomeningocele	3.4 horas (dev st. 1.1)
Uso de antibióticos profilácticos durante reparación del mielomeningocele	73 pacientes (57.9%)
Complicaciones de la reparación del mielomeningocele	26 casos (22.4%)
Ventriculitis no asociada a la derivación	16 pacientes (12.5%)
Derivación ventrículo-peritoneales	97 (100% pacientes con hidrocefalia)
Edad promedio en la cual se insertó derivación	30.4 días (dev st. 17.7)
Uso de antibióticos profilácticos durante la derivación	68 pacientes (70.1%)
Duración de la derivación	2.3 horas (dev st. 0.8)
Ventriculitis asociada a la derivación	5 pacientes (5.2%)
Muertes	0 pacientes
Tiempo promedio de hospitalización	42.2 días (dev st. 26.3)

niño o esperando para la cirugía pero se utilizan antibióticos libremente si esta indicado para otras condiciones. Luego que la condición general del niño ha sido estabilizada el servicio de neurocirugía es consultado. El cerrado del mielomenigocele se hace con urgencia (tan pronto como es posible) pero no como emergencia. La reparación del mielomeningocele se lleva acabo usando de base las técnicas estándar descritas en la literatura médica^{10, 21, 22, 27, 31-33} y amoldadas a cada caso individual. Se utilizan antibióticos profilácticamente previo a la cirugía en la sala de operaciones de acuerdo con la preferencia del cirujano. El crecimiento de la cabeza es seguido cuidadosamente y el diagnóstico de hidrocefalia se confirma con una tomografía computarizada de la cabeza. La implantación del sistema de derivación para el control de la hidrocefalia se realiza luego que se esta seguro que no existe ningún problema médico activo; usualmente luego que se evidencia que la reparación del mielomeningocele esta sanando correctamente.

El análisis de la información se llevó acabo mediante la prueba del análisis de la variación usando el Módulo Estadístico para la Ciencias Sociales (SPSSx, SSPS Inc., Chicago, Illinois) en el sistema IBM 4361-3 (International Business Machines, Boca Ratón, Florida). Una probabilidad de $P \leq 0.05$ fue considerada como significativa.

Resultados

Los expedientes médicos de 128 pacientes con el diagnóstico de mielomeningocele que fueron tratados en nuestra institución desde enero de 1980 a julio de 1985 fueron identificados y analizados retrospectivamente. Ver tabla número 1. Se identificaron 62 varones (48.4%) y 66 hembras (51.6%). El peso promedio al momento de nacer fue de 6.57 libras (desv. estd. de 1.43 libras), el peso mínimo al nacer fue de 2.31 libras, y el máximo de 10.44 libras. El defecto fue localizado en el área torácica en 3 casos (2.3%), en el área toraco-lumbar en 41 casos (32.0%), 28 en el área lumbar (21.9%) y 56 en el área lumbo-sacral (43.8%).

El tamaño de la lesión del mielomeningocele fue recopilado en 50 casos. El área promedio de la lesión fue de 29.91 cm cuadrados (desv. est. 19.5 cm cuadrados) el valor mínimo fue de 3.0 cm cuadrados y el máximo de 100.0 cm cuadrados. El escape del líquido cefalorraquídeo a través del defecto luego de nacido el niño fue descrito en 12 casos (9.4%). El defecto del mielomenigocele fue reparado en 126 casos (98.4%) durante la hospitalización inicial. El promedio de la edad al hospitalización inicial. La edad promedio al momento de la reparación del mielomeningocele fue de 6.6 días (desv. est. 7.3 días), con un valor mínimo de 24 horas y un máximo de 52.3 días. La duración de la cirugía incluyendo el tiempo de intubación y extubación de la anestesia (desv. est. 1.1 horas). Antibióticos profilácticos al momento de la cirugía del mielomeningocele fueron utilizados en 73 casos (57.9%). Complicaciones en el sanado de la reparación del mielomeningocele tales como necrosis de la piel, escape de líquido cefalorraquídeo o infección de la herida ocurrieron en 26 casos (22.4%). Se encontraron 16 casos (12.5%) que desarrollaron ventriculitis previo a la implantación de la derivación. Los organismos causantes de esta en orden de frecuencia lo fueron Klebsiella, Acetobacter, Escherichia Coli, Pseudomonas, Serratia, Staphylococcus Epidermidis, Enterococcus y especies de Enterobacter.

El promedio de la circunferencia de la cabeza al momento de nacer fue de 36.1 cm (desv. est. 4.9 cm). Se confirmó el diagnóstico de hidrocefalia durante la primera hospitalización en 97 casos (75.6%), todos ellos fueron tratados con la implantación de un sistema de derivación ventriculoperitoneal. La edad promedio al momento de la derivación fue de 30.4 días (desv. est. 17.7 días). El promedio de la circunferencia de la cabeza al momento de la derivación fue de 39.4 cm (desv. est. 4.5 cm). El promedio de duración de la cirugía de la derivación incluyendo el tiempo de intubación y extubación fue de 2.3 horas (desv. est. 0.8 horas). Se hizo uso de profilaxis de antibióticos en 68 casos (70.1%) al momento de la cirugía de la derivación. El diagnóstico de ventriculitis fue confirmado en 5 pacientes (5.2%) luego

de la implantación de la derivación. Los organismos causantes de la ventriculitis luego de la implantación de la derivación lo fueron *Staphylococcus Epidermidis*, *Streptococcus*, *Pseudomonas*, *Alcaligenes Faecalis* y *Citrobacter*.

El tiempo de hospitalización promedio fue de 42.2 días (desv. est. 26.3 días) con una estadía mínima de 4 días y una máxima de 170 días. No ocurrió ninguna muerte durante la hospitalización inicial en esta serie.

Discusión

La incidencia de mielomeningocele en los Estados Unidos de América es de 1 a 2 por cada 1,000 nacimientos vivos,^{21, 22} aunque se ha reportado una variación significativa en la incidencia en diferentes grupos étnicos. La incidencia de mielomeningocele en la población puertorriqueña se estima en alrededor de 1 a 2 por cada 1,000 nacimientos vivos (data sin publicar). El defecto en la embriogénesis que desemboca en la formación del mielomeningocele se cree que ocurre durante la cuarta semana de gestación.^{27, 34} El agente etiológico que causa el desorden de los pasos sincronizados necesarios para la formación del cordón espinal que provoca en el desarrollo de este defecto se desconoce todavía.

En 1982 McLone y asociados publicaron un estudio de gran importancia en el cual correlacionaban las infecciones en el sistema nervioso central (ventriculitis) como el mayor factor limitante en la inteligencia de los niños afectados con mielomeningocele.²⁶ Ellos encontraron que la ventriculitis reducía el coeficiente intelectual (IQ) en un 25% (IQ promedio de 72 en un grupo que había sufrido ventriculitis vs. el IQ promedio de 95 en un grupo que nunca se había infectado). En un artículo mucho más reciente McLone expresó que alrededor de un 80% de los niños afectados con mielomeningocele deben de tener una inteligencia normal.¹⁵ Convencidos que el poseer una inteligencia normal es el factor más crítico para obtener una vida independiente y productiva para el paciente con mielomeningocele decidimos examinar y comparar en detalle los diferentes parámetros disponibles entre aquellos pacientes que habían desarrollado ventriculitis y aquellos que no la habían sufrido. La ventriculitis puede ser diagnosticada en diferentes etapas durante el cuidado médico de estos niños. Puede ser identificada antes de la reparación del mielomeningocele, después de la reparación pero antes de la implantación de la derivación ventricular o después de la derivación. Los problemas de ventriculitis asociados a derivación ventricular han sido estudiados extensamente en la literatura médica.^{21-23, 26, 27, 29, 30, 35-39} Pero hay muy pocos estudios de casos de ventriculitis específicamente asociados con la reparación del mielomeningocele.^{4, 18, 19, 27} Por lo tanto en el presente estudio se examinaron en detalle todos los casos que desarrollaron ventriculitis y en especial en aquellos casos en los cuales el proceso infeccioso no estuvo directamente asociado con el procedimiento de derivación ventricular. El grupo de pacientes que desarrollaron ventriculitis antes del procedimiento de derivación fueron denominados como el grupo con ventriculitis no asociada a la derivación.

La incidencia de ventriculitis antes de la implantación

de la derivación en este estudio fue de 12.5% (16 casos). La incidencia de ventriculitis reportada en la literatura va de un 10% a un 25%.^{4, 18, 19, 27} Los organismos causantes más comunes en orden de frecuencia lo fueron *Klebsiella*, *Acetobacter*, *Escherichia Coli*, *Pseudomonas*, *Serratia*, *Staphylococcus Epidermidis*, *Streptococcus*, *Enterococcus* y algunas especies de *Enterobacter*. Se encontraron 5 pacientes infectados con más de uno de estos organismos. Estos organismos usualmente eran colonizadores del tracto gastrointestinal y de la piel. Los organismos aislados del líquido ventricular de nuestros pacientes seguían un patrón similar de los organismos encontrados en la serie reportada por Charney et al.⁴

Una de las variables más controversiales es la edad óptima en la cual se debe de reparar el mielomeningocele. El cerrado del mielomeningocele es recomendado que se haga dentro de las primeras 48 horas de nacido el niño de acuerdo con algunos autores.^{6, 7, 9, 24, 17, 25} Otros estudios no obstante recomiendan que el cerrado puede ser hecho luego de las 48 horas sin efectos detrimentales al paciente.^{1, 4, 6, 18-20} En esta serie la edad promedio al momento de la reparación del mielomeningocele fue de 6.6 días. En dos pacientes la reparación del mielomeningocele no fue realizada durante la primera hospitalización, ninguno de estos dos pacientes desarrolló ventriculitis. El promedio de la edad al momento de la reparación en los 16 casos que desarrollaron ventriculitis fue de 9.7 días y el promedio de la edad del grupo que no la desarrolló fue de 6.2 días. Esta correlación no es estadísticamente significativa ($P=0.07$). De los 16 niños que desarrollaron ventriculitis, 5 (31.3%), fueron operados en las primeras 48 horas de edad, 6 (37.5%) fueron operados entre la edad de 3 a 6 días, dos de los pacientes fueron reparados en los días 12 y 16 respectivamente, dos a los 20 días y el último a la edad de 52 días. En el grupo que no sufrió de infección al sistema nervioso central (SNC), 26% fue reparado a las 48 horas de nacidos, 44% fueron operados entre los días 3 y 6, 16% entre los días 6 y 12 y el 14% después de los 12 días de edad (los dos casos sin cirugía fueron excluidos). Ver tabla número 2. De los 16 casos con ventriculitis no asociados a la derivación, 3 de ellos fueron diagnosticados con ventriculitis antes que el mielomeningocele fuera reparado y 13 casos luego que la cirugía fuera hecha. En los 3 casos en los cuales la cirugía fue hecha luego del diagnóstico de ventriculitis, la reparación se llevó a cabo luego que la infección al SNC había sido erradicada por completo. Dos de ellos fueron operados a la edad de 20 días y el otro a la edad de 52 días. Si eliminamos estos tres casos, el promedio del tiempo de

Tabla 2

Edad en la cual se repara el defecto de mielomeningocele (días)	Grupo con ventriculitis no asociado a derivación (N=16)	Grupo sin ventriculitis (N=110)
0-2	31.3%	26.0%
3-6	37.5%	44.0%
6-12	6.3%	16.0%
>12	25.0%	14.0%

cirugía para el grupo que desarrolló infección del SNC fue de 4.7 días.

Se debe de indicar que en esta serie no se encontró que la incidencia de ventriculitis fuera modificada favorablemente por la reparación del defecto de mielomeningocele en las primeras 48 horas de vida a diferencia de lo reportado por algunos investigadores.^{7-9, 17, 24, 25} Hay un sin número de situaciones observadas por las cuales la reparación del mielomeningocele es de 6.6 días. Algunos de estos pacientes son referidos a nuestra institución varios días después que nacen, especialmente aquellos que provienen de Islas Virgenes. Otros de estos pacientes tienen otras complicaciones médicas (pulmonía por aspiración, ictericia severa, septicemia, ect.) que requieren su resolución antes de contemplar las posibilidades de cirugía. Nuestra ley local requiere el permiso de ambos padres para la cirugía, este requerimiento se convierte en un problema de logística especialmente cuando la madre esta convaleciendo luego de la cesárea en otro hospital. Siendo nuestra institución el mayor centro de trauma y cuidado supra-terciario en la isla y habiendo una gran demanda por el uso de las salas de operaciones, decidir entre si se repara un mielomeningocele o se opera un trauma a la cabeza es común en nuestro servicio.

El grupo del Hospital de Niños de Philadelphia⁴ ha recomendado el retrasar la cirugía con el propósito de permitir un período de tiempo para discutir con los padres sobre las opciones de cirugía en el manejo de los niños con mielomeningocele. Nosotros pensamos que los padres se deben de envolver en el proceso de tomar decisiones sobre el cuidado de sus niños pero tenemos grandes dudas si son capaces de comprender en un corto período de tiempo la complejidad de los problemas médicos y quirúrgicos envueltos en el cuidado multiespecializado de estos pacientes. Por lo tanto recomendamos el tratamiento quirúrgico de todos los pacientes, a menos que el neonato este seriamente enfermo y que sea incapaz de sobrevivir aun ofreciéndosele el máximo de cuidado médico.

Otra variable que se examinó fue el peso al nacer, cuyo promedio para toda la serie fue de 6.59 lbs., para los 16 casos con ventriculitis fue de 6.64 lbs. y los no infectados de 6.57 lbs. No hay significancia estadística entre estos grupos ($P=0.89$). Ver tabla 3

El tamaño del defecto del mielomeningocele fue comparado entre los grupos. El promedio del tamaño del defecto fue recopilado en 50 de los casos, 9 casos (56.3%) con ventriculitis no relacionada a la derivación y 41 casos (36.6%) sin infección. El promedio del tamaño de la lesión fue de 29.22 cm para el grupo en total, 32.33 cm para el grupo con ventriculitis y 28.80 cm para el grupo sin infección. No hay diferencia estadística entre los grupos ($P=0.58$).

En un reporte reciente por Hubballah y Hoffman (28) señalaron que los niños nacidos con hidrocefalia asociado con mielomeningocele están en un alto riesgo de escape de líquido cefalorraquídeo e infecciones del SNC. Nosotros comparamos la circunferencia de la cabeza al nacer en nuestros grupos de estudio. El promedio de la circunferencia de la cabeza al nacer para todos los niños fue de 36.1 cm, para el grupo con infección al SNS no asociada a la derivación fue de 35.0 cm y de 36.2 cm para

Tabla 3

Parámetro	Grupo con Ventriculitis No Asociado a Derivación (N=16)	Grupo sin Ventriculitis (N=110)	P
Peso al nacer	6.64 Lbs	6.57 Lbs	0.89
tamaño del defecto del mielomeningocele (N=50)	32.33 cm ² (N=9)	28.80 cm ² (N=41)	0.58
Circunferencia de cabeza al nacer	35.0 cm	36.2 cm	0.36
Escape de líquido cefalorraquídeo antes de reparación	18.8%	8.0%	0.40
Duración de reparación del mielomeningocele	3.2 horas	2.9 horas	0.17
Antibióticos profilácticos	81.3%	59.4%	0.16
Problemas de sanado de la reparación del mielomeningocele	43.8%	19.0%	0.03

el grupo sin ventriculitis. Se encontró que no había correlación estadística entre los grupos ($P=0.36$). Por lo tanto el nacer con hidrocefalia no es un factor de riesgo para el desarrollo de ventriculitis en esta serie. El escape activo de líquido cefalorraquídeo a través del defecto del mielomeningocele fue documentado en 12 casos (10.2%); en 3 casos (18.8%) que había desarrollado ventriculitis no asociada a la derivación y en 9 casos (8.0%) sin ventriculitis. Tampoco se encontró correlación estadística ($P=0.40$) en este parámetro. Ninguno de los tres pacientes que desarrollaron ventriculitis antes del cierre del defecto tenía documentado escape activo de líquido cefalorraquídeo. Este hallazgo es interesante porque esta en controversia con lo reportado en la literatura.^{18, 21, 29} Ver tabla 3.

Se ha reportado para otros procedimientos neuroquirúrgicos que el número de complicaciones quirúrgicas estan asociadas a las diferentes técnicas y habilidades del cirujano, la duración del procedimiento y otros parámetros.⁴⁰ Con esto en mente se examinó si el cirujano o el tiempo requerido para hacer la cirugía contribuía a la incidencia de ventriculitis. En nuestra institución la mayoría de los cierres de mielomeningocele son hecho por los residentes que se encuentran en los últimos años de su entrenamiento. No existe correlación entre la incidencia de infección en el SNC y cual de los cirujanos realizó el procedimiento ($P=0.29$). El tiempo total que se toma en la cirugía para la reparación del mielomeningocele fue analizado en los grupos estudiados. Este tiempo incluye desde que llega el paciente a la sala de operaciones hasta el tiempo que sale de ella. El promedio del tiempo fue de 2.9 horas para el grupo en total y de 3.2 horas para el grupo con ventriculitis no relacionada a la derivación y de 2.9 horas para el grupo sin infección en el SNC. Esta relación no era estadísticamente significativa ($P=0.17$). Por otro lado es sugestivo que los casos con alto riesgo de

desarrollar ventriculitis tienden a estar más tiempo en la sala de operaciones. Esta observación esta asociada a que el recién nacido tiene una gran área superficial por unidad de peso y es incapaz de mantener una temperatura normal en su cuerpo en un ambiente frío. Una larga exposición en la sala de operaciones favorece las posibilidades de que desarrolle hipotermia, acidosis y hipoxia²² comprometiendo la condición general del paciente y la respuesta al sanado de la herida.

La profilaxis de antibióticos en la sala de operaciones antes de la cirugía fue utilizada en 73 pacientes (57.9%). En el grupo de los que tenían ventriculitis no asociada a la derivación 13 de los 16 (81.3%) recibieron profilaxis de antibióticos. En el grupo que no desarrollaron ventriculitis solo un 59.4% recibieron antibióticos profilácticos. No existe relación estadística en relación ($P=0.16$). Estos resultados indican que el uso de profilaxis de antibióticos al tiempo de la cirugía para la internalización de una placa neural ya colonizada no ofrece protección en contra del desarrollo de ventriculitis. Algunos investigadores clínicos han dirigido sus esfuerzos a tratar de evitar la colonización de la placa neural mediante el uso de antibióticos sistémicos⁶ o posponiendo la reparación del mielomeningocele hasta que cultivos sucesivos de la placa neural sean negativos.²⁹ El uso de antibióticos sistémicos parece reducir la incidencia de ventriculitis de acuerdo a un grupo de autores.^{4, 19}

Información sobre problemas con el sanado de la herida de la espalda luego de la reparación del mielomeningocele fue recopilado en 116 de los 126 casos que fueron a cirugía. Ver tabla 3. La información estaba disponible en todos los pacientes que desarrollaron ventriculitis no asociada a la derivación. Los problemas con el cerrado de la espalda se definieron como necrosis de la piel, escape de líquido cefalorraquídeo e infección de la herida. Se encontraron 26 casos (22.4%) con estos problemas y 90 casos (77.4%) sin problemas de sanado de la herida luego de la reparación del mielomeningocele. De los 16 pacientes con ventriculitis no asociadas a la derivación se encontró que un grupo de 7 pacientes (43.8%) desarrollaron problemas con la herida de la espalda mientras que solo 19 (19.0%) de los pacientes que no desarrollaron ventriculitis tenían problemas con el sanado de la reparación del mielomeningocele. Esta observación fue estadísticamente significativa ($P=0.03$). En el grupo con ventriculitis no asociada a la derivación 3 pacientes desarrollaron necrosis de la piel, 1 paciente desarrolló escape de líquido cefalorraquídeo y 3 desarrollaron infección de la piel. La relación entre los problemas de sanado en la reparación del mielomeningocele y la ventriculitis han sido esporádicamente reportados en la literatura. En 1973 Foltz et al. reportó una incidencia de 14.0% de dehiscencia de la reparación del mielomeningocele⁶ y que esta incidencia podía ser reducida a un 3 o 5% si los pacientes hidrocefálicos eran sometidos a una derivación antes de repararles el mielomeningocele. McLone reportó un paciente que falleció luego de una dehiscencia de la reparación de la espina bífida quística.¹⁴ Lehman y sus colaboradores concientes de la importancia de la necrosis de la piel y de la dehiscencia surgieron el uso de unguento de nitroglicerina para aumentar flujo cutáneo de sangre en el

cerrado del mielomeningocele.¹⁰ Otros estudios han reportado diferentes técnicas de colgajos de piel con el propósito de evitar la tensión en los bordes de la piel y la necrosis de los mismos.^{41, 42}

Este estudio fuertemente correlaciona la incidencia de ventriculitis con las complicaciones en el sanado del cierre del mielomeningocele. No estamos concientes de otro estudio que correlacione estas dos variables tan definidamente. Se deben considerar diferentes técnicas de reparación del defecto del mielomeningocele que reduzcan estas complicaciones. Diferentes técnicas para reparación del mielomeningocele han sido reportadas.^{10, 27, 32, 33, 41, 42} La técnica ideal debe ser aquella que sea rápida y fácil de ejecutar, asociada a una pérdida de sangre mínima, evite el daño a la placa neural, disminuya el anchaje del cordón espinal y reduzca la posibilidad de necrosis de los bordes de la piel y la dehiscencia. En nuestra institución actualmente se esta llevando acabo un estudio prospectivo al azar entre las diferentes técnicas quirúrgicas para la reparación del mielomeningocele.

Se encontraron 97 pacientes (75.6%) diagnosticados con hidrocefalia durante la hospitalización inicial. Todos ellos fueron tratados mediante la implantación de una derivación ventrículo-peritoneal. La incidencia de ventriculitis luego de la implantación de la derivación en esta serie fue de 5.2% o 5 casos de 97 procedimientos realizados. La complicación de ventriculitis luego de la implantación de la derivación ventricular y los diferentes parámetros y variables que influyen han sido discutidos extensamente en la literatura médica.^{21-23, 26, 27, 29, 30, 35-38}

Contando en esta serie con tan solo 5 casos de ventriculitis luego de la derivación no podemos producir ninguna correlación conclusiva pero hay ciertas observaciones que se deben ser comentadas.

Una inspección general de los diferentes parámetros estudiados entre el grupo con ventriculitis relacionada a la derivación y el grupo que no la desarrolló falló en demostrar relación estadística entre ellos para: peso al nacer, tamaño inmediato de la cabeza previo a la implantación de la derivación, edad al momento del procedimiento de derivación, duración de la cirugía de la derivación y el uso de profilaxis de antibióticos.

Es interesante señalar que dos pacientes con ventriculitis relacionada a la derivación tuvieron ventriculitis no asociada a la derivación. Los organismos causantes de producir ventriculitis no asociada a la derivación lo fueron *Klebsiella* y *Pseudomonas* y las relacionadas a la derivación lo fueron *Acetobacter* y *Staphylococcus Epidermidis* en cada paciente respectivamente. Cabe la posibilidad que estos niños se encuentren inmunológicamente deprimidos aunque no contamos con la data científica para sostener esta observación. Por otro lado ha sido demostrado por Borges³⁵ que las derivaciones de líquido cefalorraquídeo interfieren con las defensas inmunológicas de estos pacientes.

En tiempos donde la fiscalización médica y hospitalaria se lleva acabo constantemente es importante el estimar el tiempo en que estos pacientes deben de permanecer en el hospital. El tiempo de hospitalización promedio en nuestro estudio fue de 42.2 días. Complicaciones tales como la ventriculitis son obviamente razones que

prolongan la estadía en el hospital. Por ejemplo los pacientes que desarrollaron ventriculitis no asociada a la derivación permanecieron en el hospital un promedio de 57.4 días y el grupo de pacientes que tuvieron ventriculitis relacionada con la derivación (información disponible en 4 casos) tuvieron un estadía promedio de 75.2 días.

No hubo mortalidad reportada en esta serie. Al presente hemos encontrado escasas publicaciones que estudien la sobrevida inicial de los niños afectados con mielomeningocele. El grupo del Hospital del Niño de Philadelphia reportó una mortalidad de cero en los primeros 10 meses de edad en una serie de 52 pacientes con reparación temprana del defecto de espina bífida quística y una mortalidad de un 6% en el grupo con cirugía tardía.¹⁹ Gross y asociados reportaron 100% de sobrevivencia en el grupo que recibió cuidado médico intenso (un paciente murió a la edad de 14 meses debido a un accidente de tránsito).²⁰ Es razonable el aceptar la muerte de un pequeño número de neonatos que nacen con anomalías que son incompatible con la vida o que desarrollan complicaciones que a la larga resultan catastróficas.

Conclusiones

Nuestra experiencia en el manejo de los recién nacidos afectados con mielomeningocele ha sido revisada desde el punto de vista de las diferentes variables presentes en el manejo de estos niños. La data obtenida no sostiene el concepto que el reparar el defecto de mielomeningocele dentro de las primeras 48 horas de vida disminuya el riesgo de desarrollar ventriculitis. Por otro lado se identificó que las complicaciones en la reparación del mielomeningocele (necrosis de los colgajos de piel, escape de líquido cefalorraquídeo e infección de la herida) constituye uno de los principales riesgos para el desarrollo de ventriculitis. Esperamos que este estudio tenga una contribución positiva mejorando el cuidado médico de los niños afectados con mielomeningocele.

Resumen: Los expedientes médicos de 128 niños tratados por su condición de mielomeningocele en el Hospital Pediátrico Universitario del Centro Médico de Puerto Rico durante el período de enero de 1980 a julio de 1985 fueron revisados retrospectivamente. Diferentes parámetros previamente definidos de la primera hospitalización de estos niños fueron analizados en detalle. La edad promedio a la cual se reparó el defecto de mielomeningocele fue de 6.6 días. Análisis estadístico demostró que reparar el defecto de mielomeningocele antes de las primeras 48 horas de vida no disminuye el riesgo de desarrollar infecciones en el sistema nervioso central (ventriculitis). Complicaciones del sanado de la reparación del mielomeningocele (como necrosis de los colgajos de piel, escape de líquido cefalorraquídeo e infección de la herida) estuvieron presentes en el 43.8% de los pacientes que desarrollaron ventriculitis y solo en el 19.0% de los que no desarrollaron infecciones del sistema nervioso central. Esta observación estadísticamente válida ($P=0.03$) establece que complicaciones del sanado de la reparación del mielomeningocele constituyen el factor de riesgo principal para el desarrollo de ventriculitis. Esta observación constituye una aportación significativa a la literatura médica mundial.

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ALLAN J. HAMILTON, M.D.

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Senior Thesis; recently published article, "Who Shall Live
and Who Shall Die" in Newsweek Magazine.



“The work I’m doing in the Army Reserve fits perfectly with my academic research interests in civilian life. The Army is very concerned with the effects of high-altitude cerebral edema, which is a mirror model of cerebral hypoxia, something I deal with every day in our neurosurgical intensive care unit. I couldn’t ask for a smoother transition. And that’s true for a lot of Reserve physicians. All we really do is change our clothes, not our mindset.

“Some of the projects the Army is undertaking are on the cutting edge of research. For example, I’m currently involved in developing for the Army a prototype of a non-invasive intracranial pressure-monitoring device that we hope will allow us to measure pressure changes as the brain swells—without drilling holes in the skull. If we can get our design to work, such a device could revolutionize high-altitude medicine as well as civilian neurosurgical care.

“The quality of medicine and the caliber of people I’ve been associated with in the Army Reserve are, without question, equal to civilian hospitals. In fact, I’m giving serious consideration to applying for an active duty academic position in Army Medicine when my residency ends at Massachusetts General. //

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Prevalence of Upper Gastrointestinal Mucosal Abnormalities at a Rheumatology Clinic

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Summary: The purpose of this study was to determine the prevalence and degree of upper gastrointestinal mucosal damage in patients with rheumatoid arthritis or osteoarthritis receiving non steroidal antiinflammatory drugs (NSAID's) with or without prednisone; and to determine any correlation between the drugs taken and the abnormalities.

Patients attending the Rheumatology Clinic of the University Hospital were chosen at random for participation. Eightyfive of 123 were included. Endoscopy was performed and the mucosal appearance was graded from 0 to 9. Sixteen patients had normal mucosa, while 69 (81.1%) had positive findings, the majority were minimal (51.8%). Fiftyeight of the 85 patients were symptomatic, 22 of these (30%) had moderate or severe changes, while only 3 of 27 (11.1%) asymptomatic had moderate or severe changes. Six patients (7%) had active ulcers.

Most patients on antirheumatic drugs had minimal abnormalities on endoscopy, there was no increased risk for severity of disease when prednisone was added to NSAID's. The prevalence of ulcers was not increased as compared to the general population.

The association of several musculoskeletal disorders with acid peptic disease has been previously described.¹ This association may be a primary one or related to the use of nonsteroidal antinflammatory drugs (NSAID's) or other drugs used in the treatment of these conditions. Concern has grown in recent years over the ability of many commonly used drugs to cause acute or chronic gastrointestinal injury. Most of the attention has been focused on aspirin and other NSAID's that may occasionally cause a number of clinically important gastrointestinal side effects.

Epidemiologic studies have shown a highly significant association between peptic ulcer disease and heavy intake of aspirin.²⁻⁵ Similarly, patients with rheumatoid arthritis who are treated with antiinflammatory medications have been suspected of having an increased incidence of peptic ulcer disease, but this continues to be an unsettled issue. Aspirin and certain NSAID's have been implicated as a cause of massive life threatening bleeding, however, in

the vast majority of cases the gastrointestinal (GI) side effects are limited to dyspeptic symptoms, minor mucosal damage and clinically insignificant blood loss.⁶⁻¹⁰

The damaging effect of aspirin and NSAID's on the gastric mucosa has been well documented by endoscopy,¹⁰⁻¹⁶ and by studies of fecal blood loss.¹⁷⁻¹⁹ The mechanism by which NSAID's cause GI side effects is uncertain, but all are known to inhibit prostaglandin synthesis.

This inhibition, specially of PGE₂, could be of paramount importance since this substance which is present in normal gastric mucosa, reduces gastric acid output, increases mucus and bicarbonate secretion and helps to maintain an adequate mucosal blood supply, all of which account for the integrity of the normal mucosa.

The purpose of the present study was to determine the prevalence and degree of upper gastrointestinal mucosal damage by endoscopy in patients with rheumatoid arthritis (RA) or osteoarthritis (OA) taking nonsteroidal antiinflammatory drugs with or without prednisone or other antirheumatic drugs. Also, to determine any possible correlation between drugs taken and mucosal abnormalities.

Materials and Methods

Patients attending the Rheumatology Clinic of the University Hospital were randomized using the table of random numbers and asked to participate in the study. Patients with systemic lupus erythematosus, dermatomyositis, scleroderma, and complicated collagen diseases were excluded. Informed consent was obtained in writing for each participant after the nature of the study was fully explained. A pertinent history was obtained by the medical resident rotating in our service to include alcohol intake, smoking history, epigastric pain, heartburn, nausea, vomiting, hematemesis and melena. A base line endoscopy was performed at 8:00 A.M., approximately 10 hours after the last NSAID or prednisone dose.

Endoscopy findings were graded on a scale of 0 to 9 as shown on figure 1. All interpretations and photographs were made as the endoscope was passed distally to eliminate errors that might result from artifacts caused by the instrument. An ulcer was defined in this study as an endoscopic deep, tridimensional, punchout lesion and an erosion was a shallow bidimensional lesion.

A single blind technique was employed in which the principal investigator was unaware of symptoms or medications taken by the volunteer. The 85 patients who

ENDOSCOPIC EVALUATION

FUNDUS Grade _____	ANTRUM Grade _____	DUODENUM Grade _____
GRADING SCALE		
Grade 0 - No evidence of abnormality		
Grade 1 - Diffuse erythema or edema without hemorrhage		
Grade 2 - Single submucosal hemorrhage or mucosal erosion		
Grade 3 - Two to five discrete submucosal hemorrhages or mucosal erosions		
Grade 4 - Six to ten discrete submucosal hemorrhages or mucosal erosions		
Grade 5 - More than ten discrete submucosal hemorrhages		
Grade 6 - Confluent or widespread areas of submucosal hemorrhages		
Grade 7 - Active bleeding from the mucosa		
Grade 8 - Mucosal erosions extending into submucosa		
Grade 9 - Penetrating ulcer		

Figure 1.

had endoscopy ranged in age from 16 to 76 years and the majority of patients (49) were between the ages of 39 and 59; 67 were female and 18 were male (Table 1). Sixtytwo patients had rheumatoid arthritis (RA), 19 had osteoarthritis (OA) and four had juvenile rheumatoid arthritis (JRA) (Table 2). All patients included in this study took their medications for a period longer than 3 months.

Table 1

Age and Sex Distribution of Patients Studied

Age (years)	16-38	39-59	≥ 60	Total
Male	3	13	2	18
Female	14	36	17	67
Total	17=(20%)	49=(57.6%)	19=(22.3%)	85
Range 16-76 y/o				

Table 2

Diagnosis

	RA	OA	JRA	TOTAL
Male	10	6	2	18
Female	52	13	2	67

RA - rheumatoid arthritis

OA - osteoarthritis

JRA - juvenile rheumatoid arthritis

Results

Of the 123 patients interviewed, 16 patients refused the procedure at the moment of the interview, 22 missed the appointment for the upper endoscopy. Eightyfive were

included in the study for a response rate of 61%. Of these 85; 58 were symptomatic, 27 were asymptomatic, 56 were taking NSAID's and 29 were on NSAID's plus prednisone.

Endoscopic findings

Of the 85 patients, 16 (18.8%) had a grade 0 endoscopic score or no evidence of mucosal changes, 69 (81.1%) had a positive endoscopic findings; the majority of those endoscopic findings were minimal (44 or 51.8%) (Table 3). Most of the lesions found were in the stomach (51/85 or 60%), while only 7 of 85 (8.2%) were limited to the duodenum and 11 of 85 (12.9%) were present in both the stomach and duodenum.

Table 3

Endoscopic findings				
Normal Mucosa	Minimal	Moderate	Severe	Total
(0)	(1-3)	(4-6)	(7-9)	
16 (19%)	44 (51.8%)	14 (16.5%)	11 (12.9%)	85

Correlation of symptoms and severity of endoscopic findings

Of the 27 asymptomatic patients 8 (29.6%) had a normal mucosa and 19 (17.4%) had some degree of abnormality. One of these (3.7%) asymptomatic patients had an active ulcer. Of the 58 symptomatic patients, 8 (13.8%) had a normal mucosa, 28 (48.2%) had minimal mucosal changes, 5 (6.2%) had an active ulcer (Table 4).

Table 4

Correlation of symptoms and endoscopic findings

	Mucosal Findings			
	Normal	Minimal	Moderate	Severe
Asymptomatic (27)	8 (29.6%)	16 (59.3%)	1 (3.7%)	2 (7.41%)
Symptomatic (58)	8 (13.8%)	28 (48.2%)	13 (22.4%)	9 (15.5%)

Correlation between endoscopic findings and medications

Of the 56 patients taking NSAID's, 14 (25%) were normal, 30 (53.6%) had minimal mucosal changes, 7 (12.5%) had several mucosal changes, 4 (7.1%) of them had an active duodenal ulcer and 1 (1.7%) an active gastric ulcer. Of the 29 patients on NSAID's plus prednisone, 5 (17.20%) had normal mucosa, 14 (48.3%) had minimal mucosal changes, one of them (3.4%) had an active duodenal ulcer (Table 5).

Table 5

	Mucosal Findings			
	Normal	Minimal	Moderate	Severe
NSAID's (56)	11	30	8	7
NSAID'S + PREDNISONE (29)	5	14	6	4

Discussion

This endoscopic randomized study indicates that the majority of the patients attending our Rheumatology Clinic that were taking NSAID's and/or prednisone had minimal mucosal changes. Although we did not carry on a control normal population or placebo study group, our results are similar to some studies in the literature in patients with rheumatoid arthritis and normal control subjects on NSAID's.^{10, 20, 21}

Of the 85 patients taking antirheumatic medications, 69 (81%) had positive endoscopic findings, the commonest single lesion was diffuse gastric erythema or Grade 1 endoscopic mucosal changes. Of the 56 patients taking NSAID's alone, 45 (80.3%) had positive endoscopic findings.

The clinical diagnosis of gastrointestinal lesions due to NSAID's in rheumatic disease patients based on symptoms alone is insensitive.^{1, 22, 23} This presents a clinical dilemma since bleeding and perforation often occur in the absence of warning symptoms and are associated with a high mortality rate specially in patients over sixty years of age.²⁴

In our study, the presence of symptoms does not guarantee the presence of severe mucosal changes; although it increases its probability, since 22 (38%) of those patients with symptoms were classified as such. (Table 4)

Aspirin usage has been implicated in the development of gastrointestinal bleeding in a number of studies. Jick's report of the Boston Collaborative Study²⁵ showed that 15.9% of patients admitted for upper gastrointestinal bleeding had heavy regular aspirin use in contrast to 6.9% of controls.

The small group of patients we included in this study makes it difficult to arrive to conclusions about the incidence of gastrointestinal bleeding. In our study only one patients had history and signs of gastrointestinal bleeding; this patient had 2 episodes of melena 3 week before endoscopy, and on endoscopy was found with an active duodenal ulcer, her hemoglobin level done after upper endoscopy was of 11.5 grams/dl.

Of 6 patients with an active ulcer, 5 patients had non specific gastrointestinal symptoms, only one of the patients with an active ulcer was in the therapeutic combination of an NSAID and 10 mg of oral prednisone. The overall prevalence of active ulcer in our study population was 7%. If we add 3 patients with duodenal

bulb deformity without active ulcer, the prevalence increases to 10.6%; not higher than the one expected in the general population.

In our study the presence or absence of symptoms was attending our Rheumatology Clinic who were on NSAID's NSAID's plus prednisone). In conclusion, most patients attending a Rheumatology Clinic who were on NSAID's or prednisone therapy longer than 3 months had positive endoscopic findings, mainly minimal mucosal changes.

The prevalence of active ulcer was not higher in the rheumatic disease patient than in the general population, and there was no increased risk for severe mucosal abnormalities when prednisone doses of 10 mg or less was added to NSAID's.

Resumen: El propósito de este estudio fue determinar la prevalencia y el grado de severidad de daño a la mucosa gastrointestinal superior en pacientes con artritis reumatoide y osteoartritis recibiendo agentes antiinflamatorios no esteroidales con o sin prednisona; y la correlación entre los medicamentos y las anomalías encontradas.

Pacientes de la Clínica de Reumatología fueron escogidos al azar para participar en el estudio. Ochenta y cinco de 123 fueron incluidos. La apariencia endoscópica de la mucosa se clasificó del 0 al 9. Dieciséis pacientes tenían mucosa normal, 69 (81.1%) tenían anomalías la mayoría mínimas (51.8%). Cincuenta y ocho de 85 pacientes tenían síntomas, 22 (38%) de estos tenían cambios moderados o severos; mientras que solo 3 (11.1%) de 27 asintomáticos tenían cambios moderados o severos. Seis pacientes (6%) tenían úlceras activas.

La mayoría de los pacientes recibiendo drogas antirreumáticas tenían cambios mínimos en endoscopia, y no se encontró un riesgo mayor para enfermedad severa al añadir prednisona a la terapia de no esteroidales. La prevalencia de úlceras en esta población no fue más alta que en la población general.

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Foro de Medicina Nuclear

Radionuclide Diagnosis of Osteoid Osteoma

Samuel Sostre, MD
José Vázquez, MD

Abstract: Bone pain is the main presenting symptom of the young patient with osteoid osteoma. This lesion must be accurately diagnosed and characterized so that appropriate therapy, —in this case, surgical removal of the nidus— can be instituted to relieve this very painful condition. Radionuclide bone scanning is an excellent technique to detect the tumor, even when x-rays are normal; to localize the nidus for precise curettage planning; to monitor the curettage process, determine when the entire nidus has been removed, and to follow up the case postoperatively to detect recurrences. No other known technique can contribute as much to the diagnosis and management of this disease.

Case Report

An eight-year-old male patient was admitted to the University Children's Hospital for evaluation of right hip pain. He denied trauma to the area and was otherwise asymptomatic without fever or weight loss and the pain increased by night. Blood chemistries, complete blood cell count, urinalysis and stool examinations were normal. The patient was referred for imaging studies.

Materials and Methods

Immediately after the IV injection of 10 mCi of ^{99m}Tc -methylidiphosphonate (^{99m}Tc -MDP), dynamic images of the upper femur and hip were obtained every 2 seconds for 1 minute utilizing a gamma camera. This "perfusion" study was followed by a "blood pool" image of 500,000 counts begun 1-2 minutes post injection. Delayed images

of the symptomatic region and entire skeleton were obtained for 500K with a parallel hole collimator. In addition, a 500K image of the femur lesion was obtained with a pinhole collimator.



Figure 1. Roentgenogram. The typical sclerotic lesion with a suggested central lucency is seen in the upper right femur of this patient with osteoid osteoma.

Nuclear Medicine Service, Veterans Administration Medical Center, and Department of Nuclear Medicine, University District Hospital, University of Puerto Rico School of Medicine, San Juan, Puerto Rico

Reprint request: Samuel Sostre, MD, Chief, Nuclear Medicine Service (115), V.A. Medical Center, One Veterans Plaza, San Juan, Puerto Rico 00927-5800



Figure 2a. Radionuclide "blood flow" study. Note faint increased perfusion to the area of the tumor.

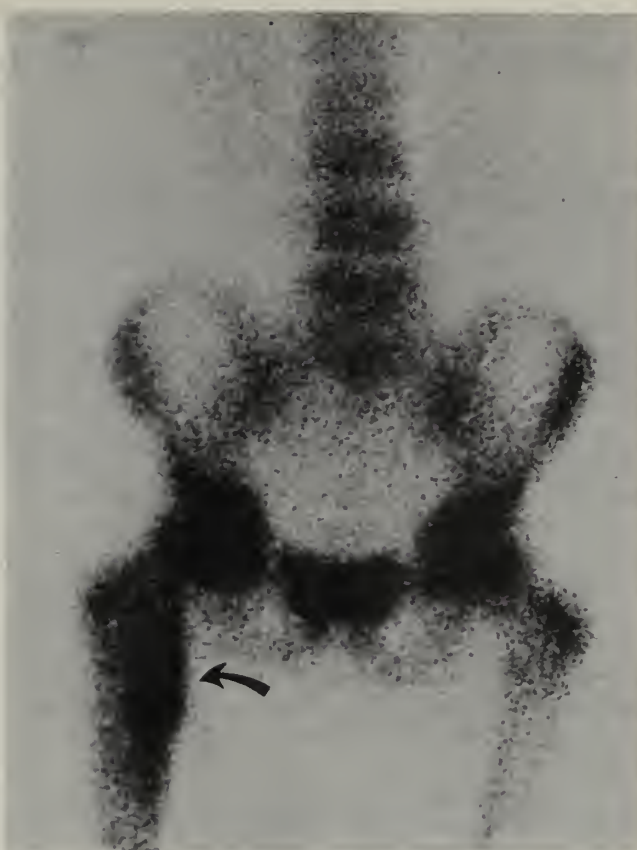


Figure 2c. Routine delayed bone scan reveals the active lesion which is most certainly causing the pain in the patient.



Figure 2b. Radionuclide "blood pool" image. Faint increased activity can also be seen in the region of the tumor.



Figure 2d. Pinhole image of the upper right femur demonstrates the typical "double intensity" appearance of an osteoid osteoma: A large active lesion (corresponding to the sclerotic area) with a round intense center (corresponding to the nidus).

Using standard techniques, roentgenograms of the upper femur and hip joint were performed.

Results

The roentgenographic study revealed a sclerotic lesion with a central lucency in the upper right femur (Fig. 1)

The radionuclide bone study showed: a) increased blood flow to the region of the lesion in the right upper femur (Fig. 2a), b) increased activity in the lesion on the blood pool scan (Fig. 2b) and c) a "hot" lesion on the delayed bone scan corresponding to the sclerotic area on the x-rays (Fig. 2c).

The pinhole image clearly showed the characteristic "double intensity" pattern of osteoid osteoma where the larger area of increased activity corresponds to the sclerotic portion of the lesion and the central focus of intense uptake, to the highly vascular nidus (Fig. 2d).

Discussion

In this patient, the diagnosis of osteoid osteoma was made with the use of the radionuclide bone scan. In addition, the nidus was clearly identified and localized, an important finding for the orthopedist contemplating surgery.

Osteoid osteoma is a fairly common abnormality comprising anywhere from 10-12% of all benign bone tumors.¹ It is most common in males, with a 2:1 male/female ratio, occurring mostly in the young, ranging from 1 1/2-23 years.² About half the cases occur in the femur or tibia. Another common site is the vertebral column, involving mostly the posterior parts of the vertebrae, such as the lamina, pedicles, facets, and spinous processes in descending frequency.³ Talus, humerus, ulna and skull are less frequent sites for this tumor.

The radiographic diagnosis rests on the identification of a focal sclerotic lesion with a central lucency in a patient with the typical symptomatology of night pain relieved by aspirin. However, the radiographic diagnosis of this tumor may be difficult in certain areas of the body, such as the spine, femoral neck region, or the small bones of the foot.² In addition, the x-ray localization of the nidus has been poor in many cases, requiring the use of CT or even angiography to visualize this highly vascular area of the tumor.^{4,5} Localization of the nidus is essential to the surgeon. If the site of the nidus is unknown, he may be obligated to remove the entire sclerotic area in block, when simple curettage of the nidus may be the only procedure necessary. Obviously, the more extensive procedure is associated with a longer postoperative recovery and higher morbidity.

The radionuclide bone scan becomes an extremely valuable test in patients with osteoid osteomas. The finding of the lesion with increased perfusion and blood pool, and the "double intensity" pattern is virtually diagnostic of the condition. It also demonstrates a higher sensitivity than roentgenograms in the detection of the lesion. In patients where the x-rays may be negative or nonspecific, the radionuclide scan will usually identify the disease.

It is also of marked utility in the localization of the nidus. It has eliminated the need for angiography and together with the CT, they have become the studies of choice for this localization.⁵

One unique utility of the bone scan is to help determine, intraoperatively, when the curettage of the nidus has been completed. As the nidus concentrates more radioactivity than the rest of the tumor, the removed nidus fragments are measured in a gamma counter. As long as the removed material is very active, fragments of nidus remain. When the activity in the curettaged tissue decreases, the entire nidus has probably been removed. Many centers are now using radionuclide counting to guide the surgery, eliminating the risk of incomplete nidus removal with its potential for recurrence.⁶

Finally, bone scans are useful in the postoperative follow up of osteoid osteoma. Recurrent pain with persistently increased activity suggests incomplete surgical resection or recurrence, and the need for reoperation.⁷

Resumen: El dolor oseo es el síntoma principal del paciente joven con osteoma osteoide. Este tumor debe ser debidamente diagnosticado y clasificado para que el tratamiento adecuado —en este caso, extirpación quirúrgica del nido— pueda ser instituido y así aliviar esta dolorosa condición. Escintigrafía de hueso es una técnica excelente para detectar el tumor, (aún cuando las radiografías sean normales para localizar el nido y planear el abordaje quirúrgico; para guiar el proceso de curetaje y determinar cuando el nido ha sido disecado en su totalidad; y para seguimiento del caso postoperatorio para detectar recurrencias. Ninguna otra técnica conocida puede contribuir tanto al diagnóstico y manejo de esta enfermedad.

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CASE REPORTS

Colonic Histoplasmosis Simulating Crohn's Disease in a Patient with AIDS: Case Report and Review of the Literature

Carmen González Keelan, MD, FCAP, FASCP
Manuel Imbert, MD

Summary: We present a rather unusual, although not unique case of a 48 year old male whose first manifestation of AIDS was chronic diarrhea simulating Crohn's disease due to colonic histoplasmosis. The patient died with disseminated histoplasmosis. We have reviewed the recent literature on Histoplasmosis as well as local reports on this subject. In view of the 30% estimated rate of infection by this organism in Puerto Rico, and knowing that dissemination of this infection occurs primarily in immunosuppressed subjects, infection with *H. capsulatum* should be thought of in our AIDS and immunosuppressed patients so that prompt a diagnosis can be rapidly determined and early therapy administered, preventing a fatal outcome.

The gastrointestinal tract is a major target organ in patients with Acquired Immuno Deficiency Syndrome (AIDS) and is affected in two thirds of these patients.¹ Besides the classic venereal diseases, a wide variety of opportunistic agents have been described infecting the gastrointestinal tract in patients with AIDS.² We report a case of a 48 year old male with chronic diarrhea, who upon autopsy was found to have disseminated histoplasmosis with colonic involvement, as well as a positive HIV test.

Case Report

A 48 year old chronic alcoholic male without history of systemic illness developed fetid diarrhea of moderate quantity, without mucus, three months prior to admission. The patient reported 6-8 bowel movements during the day, not related to food ingestion, and up to 4 movements at night. He sustained a 40 pound weight loss and developed weakness but denied fever or chills. The patient has been divorced for many years; he was in

jail seven years ago. He denies homosexual practices, drug abuse, contact with prostitutes or blood transfusions. There is no history of contact with tuberculosis or bats.

Physical examination revealed a mildly dehydrated, undernourished, chronically ill male with normal vital signs, weight of 100 pounds and height of 5'6". Two perianal fistulae were noted. Stool cultures for *E. coli*, *Shigella*, *Salmonella*, *Yersinia* and *Campylobacter* were negative. Ova and parasites were not seen. Fecal leukocytes were present. KUB and chest X-Rays were unremarkable. Sigmoidoscopy revealed several small ulcers at 13 cm with a granular and erythematous mucosa. Another ulcer was observed at 25 cm, surrounded by granular erythematous mucosa with a loss of the vascular pattern. A small bowel series and a barium enema were reported as negative. An endoscopic biopsy was performed but was superficial, showing chronic inflammation in the absence of granulomas.

Ten days after admission a miliary interstitial nodular pattern was noted on a lung x-ray. Bronchoscopy showed friability of the mucosa; no biopsy performed. Broncho-alveolar lavage fluid was negative for fungi, *P. carinii*, and acid fast bacilli. A rectal culture for *Chlamydia* was taken and the patient was started on metronidazole (Flagyl) after which he referred subjective improvement but his pulmonary condition deteriorated steadily. The rectal culture showed abundant growth of *Chlamydia trachomatis* and the patient was started on tetracycline 500 mg qid. Due to deterioration of his pulmonary condition, supplemental oxygen was needed and intravenous tetracycline was started.

Eventually the patient's deteriorating respiratory condition led to respiratory failure, requiring assisted ventilation and broad spectrum antibiotics were administered, but the patient died.

Pathology

The autopsy revealed several well delimited ulcers in the ascending, transverse, descending, sigmoid and rectal colonic mucosa. These ulcers measured from one to two centimeters in diameter and were discretely localized at intervals of one to three centimeters.



Figure 1. Segment of colon showing several well circumscribed ulcers, with unremarkable surrounding mucosa.

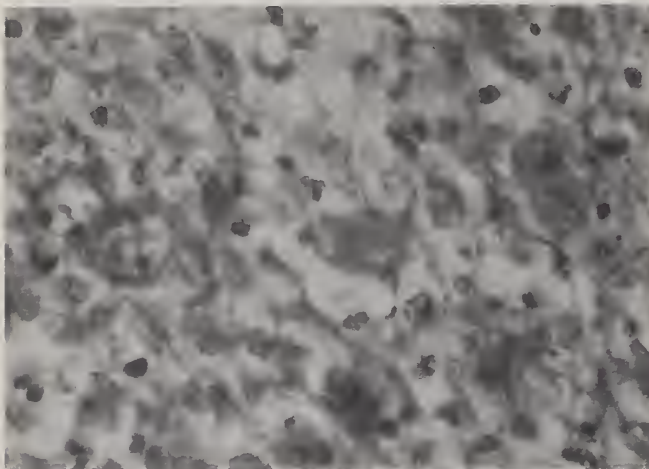


Figure 2. 40 x view of PAS stained colonic tissue, showing histiocytes loaded with *Histoplasma capsulatum*, represented by cytoplasmic deep red inclusions.

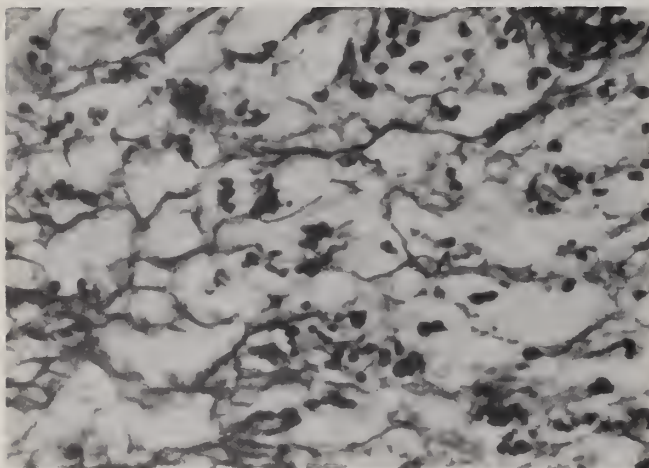


Figure 3. Methenamine silver stain of colonic tissue, showing the yeast phase of *Histoplasma capsulatum*.

Miscroscopically, necrotic areas were prominent. Abundant inflammatory exudate and numerous macrophages were seen with PAS-staining cytoplasmic organisms surrounded by clear halos. Silver stains confirmed

that the organisms were round to oval yeasts, 2 to 4 microns in diameter with occasional budding. This evidence confirmed the diagnosis of *Histoplasma capsulatum*. These histologic features were observed also in both lungs, adrenals, liver and lymph nodes. There was no residual evidence of *Chlamydia* infection at autopsy. Spleen and lymph nodes sections showed lymphocyte depletion and plasmacytosis. Micronodular liver cirrhosis with activity due to chronic alcoholism was also present. A post mortem HIV test was positive. Diagnosis of AIDS was done on the basis of a positive HIV concomitant with disseminated histoplasmosis at any site other than or in addition to lungs or cervical lymph nodes.³

Discussion

First described by Samuel Taylor Darling at the Panama Canal in 1905, *Histoplasma capsulatum* is a dimorphic fungus which grows as a mycelium in the soil and as a yeast within infected cells. The mycelium to yeast transformation of this organism is not required for the adaptation of mycelia to higher temperatures, but rather seems to be due to activation of temperature-dependent yeast-specific genes.⁴ Deriving its name from histiocytes, where the yeast form proliferates in humans, this organism probably avoids the toxic effects of superoxide anion by failing to trigger the release of the anion, rather than by inhibiting the generation of the superoxide.⁵

Perianal disease, skip areas, discrete ulcerations of the mucosa and sparing of the rectum are typical although not pathognomonic of Crohn's disease. The perianal lesions of Crohn's disease may even develop before the intestinal disease ensues.⁶ It is rather unusual for the first clinical manifestation of disseminated histoplasmosis to occur in the gastrointestinal tract, although 70% to 90% of the autopsies of patients with fatal disseminated histoplasmosis disclose involvement of the gastrointestinal tract. Our patient had perianal disease, discrete ulcers at endoscopy and chronic diarrhea of three months duration and upon admission had an unremarkable x-ray of the lungs. A clinical picture highly suggestive of Crohn's disease.

Human infection by *H. capsulatum* occurs almost entirely through pulmonary inhalation being the lung the site of primary infection and reinfection. However, there is little evidence supporting or against primary infection through the gastrointestinal tract.⁷ Alberti-Flor⁸ recently reported a case of a patient with Job's syndrome, whose only manifestations occurred in the colon, mimicking Crohn's disease. When the colon is infected with *H. capsulatum*, the ileum and the proximal colon are the most commonly involved areas. Grossly, the lesions may form elevated plaques, polyps or ulcerations.

Although histoplasmosis has seldom been reported in the Caribbean zone,^{9, 10} Sifontes et al,¹¹ estimated that one third of the Puerto Rican population has been infected with this organism. Mandell¹² reported five cases of disseminated histoplasmosis in AIDS patients who had emigrated from Puerto Rico, the Dominican Republic and Colombia. He pointed out that histoplasmosis should be suspected in AIDS patients with unexplained fever who have lived or are natives of the

Caribbean basin or South America.

In the Puerto Rico Medical Center's series of autopsies of patients with AIDS, histoplasma infection was found in up to 25% of cases, closely coinciding with the Sifontes estimated rate of infection in our population. Our case was the only one in our series presenting the symptomatology of chronic diarrhea as the first manifestation of disseminated histoplasmosis.

Since the growth of *H. capsulatum* may take weeks, waiting for culture results before instituting therapy is almost always fatal for the patient. Prompt diagnosis can be done using immunoperoxidase methods for identification of the organism in tissue biopsies.¹³

Recommended therapy for disseminated histoplasmosis in patients with AIDS is amphotericin B followed by long term prophylaxis with ketoconazole.¹⁴

Resumen: Hemos presentado el caso poco usual, pero no único, de un varón de 48 años cuya primera manifestación de SIDA fue diarrea crónica simulando enfermedad de Crohn secundaria a histoplasmosis colónica. El paciente murió con histoplasmosis diseminada. Hemos repasado la literatura reciente tocante a histoplasmosis, al igual que aquella literatura local referente a este tema. En vista de que la razón estimada de infección por este organismo es de 30% en Puerto Rico y, conociendo que los sujetos inmunosuprimidos se encuentran en un riesgo alto de que la infección se disemine, debemos pensar en *H. capsulatum* como agente infeccioso en nuestros pacientes con SIDA, de manera que hagamos un diagnóstico temprano y administremos el tratamiento adecuado prontamente, evitando así resultados fatales.

Acknowledgement

The author is grateful to Dr. Irma Rivera, Pathology Resident who performed the autopsy, to Dr. Román Vélez who helped in the diagnosis, to Dr. Consuelo Climent who reviewed the manuscript, to Ms. Zulma Albertorio who typed it and to Mr. Juan Caloca who did the photographs.

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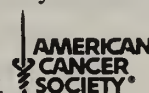
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Segundo Simposio de SIDA para Profesionales de la Salud

El Segundo Simposio de SIDA para Profesionales de la Salud es auspiciado por el Recinto de Ciencias Médicas de la Universidad de Puerto Rico y los Institutos Nacionales de Salud. Dicha actividad se llevará a cabo el miércoles 3 de agosto de 1988 en el Centro de Convenciones del Condado. Colaboran como auspiciadores, la Comisión Puertorriqueña para la Celebración del Quinto Centenario del Descubrimiento de América y Puerto Rico, el Departamento de Salud de Puerto Rico y la Fundación SIDA.

El objetivo de este Simposio es proveer a los Profesionales de la Salud con la información más reciente relacionada con la prevención y tratamiento del Síndrome de Inmunodeficiencia Adquirida (SIDA). Los temas a desarrollarse en la actividad se expondrán desde la perspectiva de la salud pública en sus diversas manifestaciones como son los aspectos legales, económicos y éticos en la prevención y tratamiento del SIDA. Distinguidos profesionales del ámbito internacional y local componen la facultad de esta actividad.

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COMUNICACIONES BREVES

El Manejo Interdisciplinario del Maltrato de Menores ante la Ley y el Tratamiento Actual

Brenda Mirabal, MD, MPH

El maltrato de menores se define como acciones u omisiones de parte de los padres o encargados de un menor de 18 años que resultan perjudiciales a su salud física, mental o emocional. El maltrato de menores incluye negligencia y abuso físico, sexual y/o emocional.¹

En Estados Unidos, se refirieron 1.5 millones de casos sospechosos de maltrato a las agencias de protección de menores en 1983.² Se estima que en Estados Unidos, 2,000 niños perecen anualmente como resultado del maltrato.³ En Puerto Rico, se reportaron 8,900 casos sospechosos de maltrato de menores a Servicios Sociales en el año fiscal 1986-1987⁴ y se estima que existen tres casos por cada uno que es reportado.⁵ Por lo tanto, aproximadamente 30,000 niños sufren de negligencia, abuso físico, sexual o emocional anualmente en la Isla.

La Ley de Protección de Menores (Ley 75 del 28 de mayo de 1980) de Puerto Rico,¹ obliga a todo profesional que trabaja con niños a reportar casos sospechosos de maltrato de menores. En adición, el org. al Departamento de Servicios Sociales la autoridad y la responsabilidad de investigar estos casos e intervenir para asegurar el bienestar de estos niños. La aprobación de esta ley fue un paso importante hacia la protección de los niños que sufren maltrato o negligencia. Sin embargo, debido a la complejidad del problema, urge una revisión de la ley, del proceso legal y en adición, de la intervención y seguimiento en estos casos. Más importante aún, debemos dirigir mayores esfuerzos hacia la prevención del maltrato y la violencia familiar.

La situación familiar que predomina en estos hogares maltratantes es muy compleja. Los padres frecuentemente han sido víctimas de abandono o maltrato en su niñez y tiene una baja estima propia. Característicamente, viven aislados socialmente y a menudo tienen un nivel de estrés³ debido a problemas serios tales como: vivencias inadecuadas, desempleo, divorcios, pobre utilización de los recursos de la comunidad y movilidad excesiva. Existe una disfunción familiar que no les permite resolver sus múltiples problemas y crisis adecuadamente, y en estas circunstancias, se precipita la violencia familiar.

En adición, existen factores de alto riesgo que hacen a un niño más susceptible al maltrato: defectos congénitos,

un temperamento difícil y un embarazo no deseado.³ Sin embargo, con frecuencia, el maltrato ocurre indiscriminadamente hacia todos los niños en el hogar.

El maltrato de menores no tiene barreras étnicas, socioeconómicas, raciales o religiosas. Por lo tanto, el criterio más importante para identificar niños víctimas de maltrato es un alto índice de sospecha.

Desgraciadamente, el abuso del niño ha ocurrido por un tiempo prolongado previo a ser identificado. Por lo tanto, es crucial que ocurra una intervención temprana y efectiva en estos casos debido al impacto de estas experiencias negativas en el desarrollo mental, emocional y físico del menor. Existen varios estudios que demuestran retraso en el desarrollo cognoscitivo, motor y el lenguaje de niños abusados.⁶ Otros estudios sugieren que el desarrollo emocional se ve afectado en áreas como: la autoestima, el manejo de la agresividad y las relaciones interpersonales (incluyendo la habilidad para confiar en otras personas).⁶ Mientras más pronto se interrumpa el maltrato, mejor es el pronóstico para ese menor, si no ha ocurrido daño irreversible.

Debido a la complejidad de la situación familiar, los problemas de salud que puede presentar el menor y la necesidad de una intervención interagencial a largo plazo, se recomienda el manejo interdisciplinario en estos casos.⁶ Esto conlleva una comunicación efectiva entre los diferentes profesionales que intervengan en el tratamiento y seguimiento de los menores afectados.

El Programa Biosicosocial para Niños Maltratados del Hospital Pediátrico Universitario comenzó a operar en agosto de 1986, con fondos federales para Víctimas del Crimen, del Departamento de Justicia de Puerto Rico. El propósito del programa es ofrecer un cuidado ambulatorio integral, a largo plazo, a niños víctimas de maltrato. Los casos provienen mayormente de la Sala de Emergencia, pacientes hospitalizados y de las clínicas ambulatorias del Hospital Pediátrico Universitario, la única facilidad en Puerto Rico que ofrece servicios médicos terciarios a niños menores de 17 años.

El programa tiene un equipo interdisciplinario compuesto por una Trabajadora Social, una Psicóloga, una Educadora, un Pediatra y un Psiquiatra de Niños y la Directora de Trabajo Social del hospital como consultores. Es el primer programa en Puerto Rico que ofrece cuidado médico como parte del manejo interdisciplinario de niños víctimas de maltrato. El programa ha recibido

155 referidos hasta fines de marzo de 1988, de los cuales se confirmó el diagnóstico en aproximadamente 85% de los casos. Los diagnósticos más frecuentes son: negligencia (50.8%), abuso combinado (24.6%), abuso sexual (13.8%) y abuso físico (7.7%). El abuso emocional sólo constituye el 3.1% de los casos confirmados.⁷

La intervención del equipo interdisciplinario incluye la evaluación médica, social y psicológica de los menores, intervención en crisis, terapia individual y terapia de juego, sostén en el proceso judicial, orientaciones en aspectos del cuidado del menor e intervenciones psiquiátricas con la familia, en algunos casos. Los pacientes y familias que necesitan un tratamiento psiquiátrico prolongado son referidos al servicio de Salud Mental.

El equipo interdisciplinario colabora continuamente con numerosos profesionales de Servicios Sociales, el Departamento de Instrucción Pública, Salud Mental, la Policía, el Sistema Judicial, Centro de Ayuda a Víctimas de Violación, Casa Protegida Julia de Burgos y otros. La calidad y dedicación de los recursos humanos de la comunidad, que están ofreciendo servicios a estas familias es sobresaliente.

Sin embargo, existen problemas a varios niveles, a saber:

- 1) *Pobre coordinación de servicios*-Muchas agencias trabajan independientemente causando demoras prolongadas en los servicios, que podrían evitarse con una mejor coordinación y comunicación interagencial.
- 2) *Se necesita legislación que proteja al menor de mayor victimización durante el proceso legal*-No se permite utilizar entrevistas grabadas (en video o grabadora) o las declaraciones que se han obtenido por profesionales que han entrevistado a la víctima, en sustitución de las declaraciones de la víctima en corte. Esto expone al menor a mayor trauma y sentimientos de culpabilidad. Frecuentemente, esto resulta en que los casos no sean procesados y el victimario continúe su mismo comportamiento.
- 3) *Ausencia de legislación o mecanismos que obliguen a los padres maltratantes a recibir tratamiento*-Muchos de estos padres rehúsan tratamiento o se ausentan a las citas de seguimiento y no existe un mecanismo legal que los obligue a asistir.
- 4) *Preferencia por las remociones voluntarias aún en casos que demuestran evidencia clara de maltrato y pobre potencial de rehabilitación*-Es más efectivo que en estos casos se realicen las remociones por la Ley 75 de 1980. Esto facilita la ubicación permanente del menor en el futuro.
- 5) *Disposiciones de ubicación permanentes demasiado lentas*-Esta situación permite que se desarrollen unos lazos afectivos estrechos entre el niño y sus padres de crianza, para luego reubicar este niño, creándole confusión y mayor trauma emocional. La ubicación permanente del menor no debe prolongarse más de seis a doce meses.
- 6) *Proceso de adopción muy lento aún en casos meritorios*-La legislación y el proceso de adopción deben ser revisados para facilitar la ubicación

permanente del menor que ha sido removido de su hogar.

- 7) *Ausencia de un currículo escolar uniforme que incorpore medidas de prevención del maltrato*-Este currículo debe comenzar desde los grados primarios.
- 8) *Recursos económicos limitados*-La industria y el sector privado tienen que involucrarse y proveer sostén económico a los programas que ofrecen servicios a estas familias maltratantes.

La identificación e intervención temprana y el seguimiento integral a largo plazo son cruciales para el manejo efectivo del abuso de menores. El instrumento más eficaz para combatir la violencia familiar es, sin duda, la prevención. Si queremos lograr cambios y mejoras en el manejo y prevención del maltrato de menores, los profesionales de la salud y la comunidad tienen que unirse y colaborar juntos.

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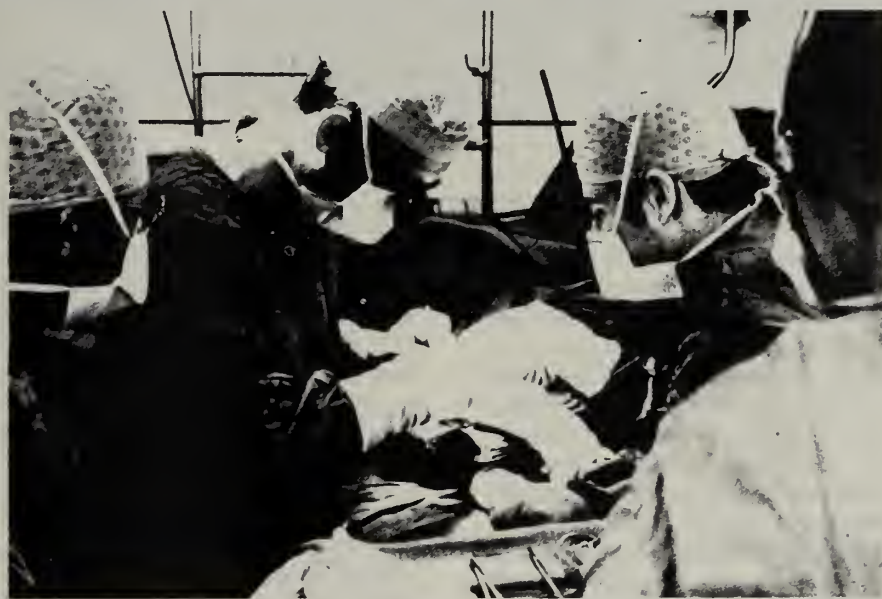
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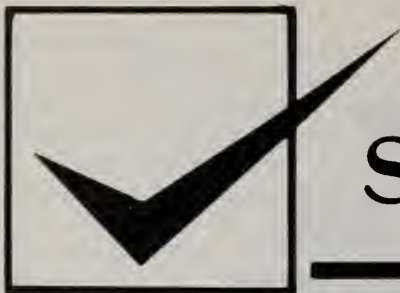
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SPECIAL ARTICLES

Human Growth Hormone and Creutzfeldt-Jakob Disease*

In 1958 scientists demonstrated that children who were deficient in growth hormone began growing when treated with human growth hormone (hGH) extracted from pituitary glands. At the time, human pituitaries were the only source of the hormone. Pituitary hGH was used effectively for more than 20 years to help growth hormone deficient children.

From 1963 to 1985 a government funded program distributed pituitary hGH to children with short stature from hGH deficiency. This program was called the National Pituitary Agency until 1983 when the name was changed to the National Hormone and Pituitary Program (NHPP). The NHPP was set up to coordinate the collection of pituitary glands removed at autopsy and to distribute hGH and other hormones extracted from these glands. It is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a part of the Federal Government's National Institutes of Health (NIH). About 7,000 patients have been treated with the NHPP-distributed growth hormone.

In late February and early April of 1985, government health officials were notified that first one, and then two more men in their twenties and mid-thirties who had been treated years before with human growth hormone supplied by the NHPP, had died. All three men had symptoms of a neurologic disorder called Creutzfeldt-Jakob disease (CJD). Pathologists confirmed this diagnosis in all three cases by careful microscopic examination of brain tissue from the men. Because CJD is so rare in young adults, the reports of three deaths from CJD in this patient group led scientists to conclude that the men who died had contracted CJD due to inadvertent contamination of growth hormone. The government's distribution of hGH was stopped.

Two commercial companies, Serono and Kabi Vitrum, also distributed pituitary-derived hGH in this country during the past decade. The methods used by the private companies to make hGH were similar to those that the NHPP used to produce hormone after 1977. At least 2,500 to 3,000 individuals are estimated to have received hormone from commercial sources. (Many of these people also received HNPP hormone.) Shortly after the

NHPP stopped distribution of hGH, these companies also ceased distributing the hormone in the U.S.

Since the first three cases of CJD were identified in U.S. recipient of growth hormone, two additional cases have been reported in this country and two overseas. Both Americans had received NHPP hormone. One died of CJD, while the other died of unrelated causes but was later found to have CJD infection based on microscopic examination of the brain. One overseas case involved a person who had received pituitary hGH prepared in a laboratory supported by the British government. The other overseas case involve a person in New Zealand who had received hGH processed in a U.S. laboratory that produced hormone for the NHPP. A pooled supply of pituitary material was used to prepare hormone for distribution in the United States and New Zealand.

What is Creutzfeldt-Jakob disease?

Creutzfeldt-Jakob disease, or CJD, is a nervous system or brain disease. It is transmitted by a particle similar to a virus. This particle, or infectious "agent," is different from the viruses most of us are familiar with. In fact, it has not yet been completely characterized. Unlike most viruses, a person infected with the CJD agent may harbor the agent for many years before becoming ill. For that reason, CJD is called a "slow-virus" disease.

What are the effects of CJD?

CJD may progress differently in different people, and it may mimic other neurologic diseases. Symptoms that may be seen in CJD include difficulty in balance while walking, loss of muscular coordination, slurred speech, failing vision, and muscle jerking, rigidity or stiffness.

These physical changes—as opposed to mental one—have been prominent in the cases of CJD reported in hGH recipients. Changes in behavior and mental capacity also occur. These changes may include dementia, inappropriate or abnormal behavior, progressive memory loss, and confusion. (Headaches are not usually a symptom of the disease.)

The symptoms of CJD are unmistakably severe and progressive. Therefore, mild, transient clumsiness, irritability or forgetfulness should not be a cause for worry. In most people with CJD, these changes progress rather rapidly over a period of several months, and the disease is usually fatal in less than a year.

*Reprinted from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, December 1987, Washington, DC.

Is there any treatment for CJD?

There is no treatment that will cure or slow the progress of CJD.

How is CJD transmitted?

A few people have been infected by direct contact with contaminated tissue or instruments in the course of surgical treatments. For example, CJD has been reported in an individual who received a transplant of the cornea from a person who was later found to have the disease; in a person who received a transplant of dura mater, a tissue that covers the brain and spinal cord; in people who had electrodes implanted in brain tissue, after the electrodes had been similarly implanted in the brain of a patient with unrecognized CJD; and in a few people who underwent neurosurgical procedure in which infection probably occurred from contaminated instruments.

In the vast majority of cases, the mode of transmission of CJD is unknown. It is known, however, that it is not transmitted through casual contact or through sexual intercourse, because husbands and wives of patients with CJD are not at increased risk of developing the disease.

Why do we believe that CJD is associated with growth hormone?

CJD is extremely rare. Worldwide, there is about one case per year per million people, and nearly all of these cases are in older individuals. Prior to reports of CJD connected with growth hormone, there had been only nine cases of the disease known to have occurred in patients younger than 30 years old.

Over the years, approximately 7,000 Americans have received hGH through the NHPP for growth hormone deficiency. Because CJD is so rare in younger people, the chances of CJD occurring by coincidence in 5 out of 7,000 individuals who received growth hormone are vanishingly small (less than 1 in 1 trillion).

There is very little doubt that the five young adults who died were exposed to the CJD agent through injections of pituitary hGH. One important goal of current scientific studies is to determine whether cases of CJD in hGH recipients will be limited to those already reported.

How would the CJD particle have gotten into supplies of hGH?

For over 20 years, the only source of hGH was human pituitary glands. The pituitary is attached to the brain, the primary target of CJD. The glands were collected from cadavers, and the growth hormone was extracted using chemical procedures. Individual pituitary glands yield only small amounts of growth hormone, so that hundreds or even thousands of glands are used to make one batch of distributed hormone. While CJD is extremely rare, we believe that one or more individuals from whom pituitaries were taken to make hGH had undetected CJD. Although efforts were made to exclude pituitaries from individuals with certain infectious brain diseases such as encephalitis and meningitis, CJD was not a specific criterion for exclusion. Also, someone

infected with CJD could have died of unrelated causes with no symptoms of CJD.

Does it make any difference whether someone received pituitary hGH prepared before or after 1977?

Around 1977, scientists began using methods of extracting pituitary hGH that yielded a more highly purified hormone than was produced before 1977. All five people in the United States in whom CJD was identified received hGH that was produced before 1977. One of these patients received hormone produced after 1977 as well.

While the methods of preparation of pituitary hGH used since 1977 yield a product that is more than 95 percent pure, there is no certainty that the modern preparation is safer than the hormone extracted before 1977. It is important for medications to be as highly purified as possible. The more effective the purification process, the less likely a medication is to cause allergic or toxic reactions. The infectious particle that causes CJD, however, is very small and extremely difficult to destroy or inactivate. The particles resist treatment with chemicals like formalin, hydrochloric acid, and alcohol. Extraction methods that result in 95 percent chemical purity still may not remove or inactivate the CJD agent.

In an effort to determine whether hormone extraction methods would eliminate the CJD agent, the British Medical Council performed an experiment in 1980 in which they deliberately introduced a slow virus similar to the CJD agent into growth hormone preparations. (They used the infectious particle for scrapie, a disease of sheep). Then they purified the preparation using routine procedures for hGH preparation similar to those used by the NHPP since 1977, and the product was tested in scrapie-susceptible animals. No infection resulted, indicating that the purification steps had indeed removed most or all of the scrapie particles. Although encouraging, this study is not a guarantee that all the infectious particles had been removed or that all pituitary hGH produced after 1977 is safe.

Is there a diagnostic test for CJD?

There is no test that can determine whether a healthy person is incubating the disease. One of the goals of research on CJD is to develop a diagnostic test that can detect infection in someone with no symptoms. A spinal fluid test has recently been developed that may aid in the diagnosis of patients with symptoms of CJD. At this time, however, this test can only help confirm the diagnosis of CJD in someone who already has symptoms that suggest the disease.

Why don't we know more about CJD?

Only in the late 1950's did scientists begin to suspect that certain neurologic disorders might be transmitted by an infectious agent distinct from any known virus. It was not until the late 1960's that CJD was recognized as a condition that was transmitted by a virus-like agent. Several teams of scientists are working to identify the infectious particle that causes CJD, as well as other slow-virus diseases. There is evidence that such an infectious

particle may be smaller than and unlike any virus known up to this time. Scientists are studying transmission of the disease, developing accurate methods of detecting it, and searching for methods to inactivate the slow-virus agent.

**I (or my child) have been treated with pituitary hGH.
What should I do now?**

Stay in touch, if possible, with the physician who prescribed the growth hormone. If that is not possible, contact one of the organizations that has an interest in hGH and hGH research. The addresses of the Human Growth Foundation and the Parent Council for Growth Normality are listed at the end of this fact sheet. These groups will relay new information to members. You can also call the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland, with questions. The number is (301) 496-3583.

Are there any measures a recipient of pituitary hGH may take to protect his or her health or that of others?

There is no reason for a person who has received pituitary hGH to make any changes in day-to-day living, health habits, interaction with family members and sexual activity, or general attention to his or her own health because of fear of CJD.

The only exception to this advice relates to donation of blood or of other tissues and organs for transplantation, because there is no way of testing to detect infection with CJD, blood banks will not collect blood from anyone who has been treated with pituitary hGH. This recommendation reflects the great caution with which the blood banking community handles selection of blood donors. It is also recommended that pituitary hGH recipients not donate other tissues or organs for transplantation.

This recommendation has no bearing on an hGH recipient's day-to-day life and interaction with others. Experts in CJD believe there is no danger of infection to family members if a person were to be incubating CJD or had active disease. Husbands and wives of patients have no increased risk of contracting the disease. CJD is not transmitted through sexual contact, and it is not transmitted from a mother to her unborn baby across the placenta.

In summary, there is no reason for someone to take any special precautions with a friend or family member who has received pituitary hGH.

What are the chances that someone who has received pituitary hGH over the years has been exposed to CJD and may become ill?

Unfortunately, there is no way for us to know that at this time. In order to answer this question, we need to know how likely it is that the CJD agent was present in the batches or lots of hGH. We need to know how likely it is that someone exposed to the agent will contract the disease and whether the dilution of the particle in growth hormone preparations affects the likelihood of infection. We also need to know if people differ in their susceptibility to contracting this disease.

To date, there have been five cases reported out of an approximate total of up to 10,000 people in this country who believed to have received pituitary growth hormone from any source. One of the five died of causes unrelated to CJD but was found to have evidence of infection based on microscopic examination of the brain. Because CJD has a long incubation period, it is too early to tell whether additional cases of the disease will develop in persons who received pituitary hGH.

What is being done to answer these questions?

To help determine the extent of contamination of pituitary hGH by CJD, samples of all available lots of hGH used by the NHPP have been inoculated into experimental animals. The animals have been followed 2 1/2 years without signs of infection and will be watched for at least 5 years for signs of the disease. This kind of testing, called a bioassay, is the most reliable way to test for contamination with the CJD infectious agent. A negative results, however, may only mean that the particular vials tested contained no virus, whereas another vial in the same lot that was given to a patient could have contained virus.

The scientists carrying out this study are more the world's leading experts in slow-virus diseases. This group of scientists also used new techniques in an attempt to detect a protein-containing filament that is characteristic for CJD in hGH preparations and in blood taken from individuals who have had hGH. While no evidence of contamination has been found, these methods of detection are not as sensitive as the bioassay, and a failure to find contamination using them would not prove that there was no contamination.

Separate from this laboratory effort is an epidemiology study that is gathering information on the health status of as many people as possible who received hGH distributed through the NHPP. The study is aimed at determining if there have been any cases of CJD other than those that have already been identified. In addition, the study will also attempt to follow hGH recipients for several years in order to track any future cases of CJD in this group.

This study is possible because the physicians who distributed NHPP growth hormone had to keep records of patients who received the hormone. The commercial companies who marketed growth hormone once it was approved by the Food and Drug Administration (FDA) were under no obligation to keep records of the users of growth hormone—just as they are not required to keep records of users of other prescription drugs. However, many recipients of pituitary hGH from commercial sources may be traced through the epidemiology study because many of these individuals received NHPP hormone as well as the commercial product.

Through the epidemiology study, we hope to provide patients who received pituitary growth hormone with an estimate of their risk of developing CJD. Two of the NIH Institutes, the NIDDK and the National Institute of Child Health and Human Development, are funding this study.

Scientists from the government's Centers for Disease

Control (CDC), the FDA, and NIH, together with a panel of advisors from the academic community who are experts in pediatric endocrinology, neurology, virology, and epidemiology, are participating in designing and carrying out the study.

I understand that a biosynthetic form of hGH is available. How is it different from the previously used hGH?

Cells in the human body make hGH using inherited instructions. These instructions, or genes, are composed of the molecule DNA. Scientists have succeeded in inserting the DNA sequence that determines the structure of hGH into the DNA of bacteria. The bacteria are a type found normally in the human digestive tract. By a process called biosynthesis, the bacteria make hGH using the inserted human DNA as a blueprint. The hormone is purified so that no bacteria are present in the hormone used for treatment.

In 1985 the FDA approved the first biosynthetic growth hormone for use in children with growth deficiency. This hormone is identical to human growth hormone except for one extra amino acid. (Amino acids are links in the chemical chains that form proteins—hGH is a protein that is 191 amino acids long). In March 1987, a second form of biosynthetic growth hormone that does not have the extra amino acid, became available commercially. Other companies are continuing to develop new biosynthetic forms of hGH.

Is biosynthetic growth hormone as effective as pituitary hGH?

In order for a drug, in this case biosynthetic hGH, to be approved by the FDA, the firms that market the drug perform clinical tests to establish that it is both effective and safe. In tests in which patients with growth hormone deficiency were treated with one or the other type of biosynthetic hGH, biosynthetic growth hormone, stimulated growth in exactly the same manner and to the same extent as pituitary hGH.

Is biosynthetic hormone safe?

Because biosynthetic hGH is not made from human tissue, there is no chance of contamination with the CJD infectious particle.

Clinical tests of biosynthetic hGH before it was marketed sought to identify any adverse effects associated with the hormone. In particular, it was important to know whether recipients would react to the extra amino acid in the first available form of biosynthetic hormone, or to the minute amounts of impurities left after the biosynthetic process in either type of biosynthetic hGH.

A person's immune or disease-fighting system can recognize substances that are not identical to anything the body itself produces. The immune system may respond to a foreign substance, such as a hormone, by making antibodies to remove or inactivate it. There was some concern that antibody response might inactivate the biosynthetic growth hormone.

Although antibody formation sometimes occurs, only very rarely do the antibodies interfere with the growth-promoting effect of biosynthetic growth hormone. Antibody formation stops when biosynthetic hormone is stopped. (Antibody formation also occurred with pituitary hGH, usually without effect, but occasionally interfering with the hormone's ability to promote growth.)

As research continues, production methods improve. The biosynthetic hormones now being used are more highly purified than the first such hormone that was clinically tested. In other words, they contain more hormone relative to the very small amount of material that remains from the biosynthetic process. Children in the clinical tests of these more highly purified hormones have had lower levels of antibodies to injected hGH than were found in the first clinical trials with biosynthetic hGH.

In summary, no major or health-threatening side effects have been associated with biosynthetic hGH use.

We were told that pituitary hGH was safe, too. How can we be sure that biosynthetic hGH is safe?

When the FDA approves drugs for use, the decision is based on the best available knowledge of the risks and benefits of the medication. This judgment is made within the limits of the capabilities of clinical testing and current understanding of how medications work. Unfortunately, it is not possible to guarantee that any medication will be 100 percent safe.

However, at least 6 years of records beginning from the first patient tests of biosynthetic hGH are now available. From this evidence, there is no reason to believe that biosynthetic hGH will cause serious or long-term health problems.

Will the NHPP distribute biosynthetic hGH at no charge for patients in research studies as the program did pituitary hGH?

No. When the NHPP was established, the only source of hGH was human pituitaries. Because of the limited supply of human pituitaries, a central resource was needed to ensure that the largest possible number of glands were collected and that hormones were systematically extracted and made available to patients for treatment under approved research protocols. With the development of biosynthetic hGH, the supply of hGH is no longer limited.

Years of clinical research have documented the effectiveness of hGH in stimulating the growth of children with hypopituitarism. There are still important needs for research with growth hormone, and NIH continues to support research in this area. NIDDK continues to distribute pituitary-derived growth hormone to scientists for nonclinical laboratory research. NIDDK does not plan to purchase biosynthetic growth hormone for distribution for clinical research. Drug companies provide biosynthetic hGH to scientists who are working on specific clinical research projects.

Can biosynthetic hGH be covered under Medicaid or private health insurance?

Human growth hormone is an FDA-approved drug. Under Federal guidelines, approved drugs can be covered under Medicaid benefits. Each state has its own guidelines for eligibility for health benefits. The best way to investigate this coverage is to contact the state health or social services department, or Medicaid office.

Private insurance coverage depends on the individual policy. If you have not already done so, discuss insurance coverage of biosynthetic hGH treatment with your insurance carrier and the doctor responsible for your child's treatment.

Additional Reading

A list of papers published in the scientific literature on hGH and CJD is available on request from the National Institute of Diabetes and Digestive and Kidney Diseases (see address below).

Other Resources

If after reading this fact sheet, you have concerns or questions, please call:

National Institute of Diabetes and
Digestive and Kidney Diseases
Building 31, Room 9A04
Bethesda, Maryland 20892
(301) 496-3583

Other resources on the subject include:

Food and Drug Administration
Division of Metabolism and
Endocrine Drug Products (HFN-810)
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857
(301) 443-3510

Human Growth Foundation
Montgomery Building
4720 Montgomery Lane
Bethesda, Maryland 20814
(301) 656-7540

Parent Council for Growth Normality
2899 Camelia Drive
Opelousas, Louisiana (70570)
(318) 942-9700

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ACTIVOS

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MEDICAL ASPECTS OF NUTRITION

Recommendations for Treatment of High Blood Cholesterol the National Cholesterol Education Program Adult Treatment Panel*

Nancy D. Ernst, MS, RD**
John C. LaRosa, MD***

Deaths from coronary heart disease (CHD) are declining. Current data indicate that from 1963 to 1985, the age-adjusted CHD death rate dropped by 42%.¹

Analysis of factors influencing the decline in CHD attributes 30% to reductions in plasma cholesterol levels.² Despite this decline, CHD still accounts for more deaths each year than any other disease, including cancer. Over one and a quarter million heart attacks occur each year, more than two-thirds in men; over a half-million people die as a result.³ More than a quarter of CHD deaths in men occur before age 65. Sixty percent of the annual heart-attack deaths occur as sudden deaths or outside a hospital before medical treatment can be provided.⁴ Clearly, there is justification for health professionals to focus on the prevention of CHD by identifying persons at high risk and encouraging them to reduce high blood cholesterol, to control high blood pressure and to stop cigarette smoking.

Blood Cholesterol Level and CHD

The evidence for a causal link between high blood cholesterol levels and CHD has been established by epidemiologic, clinical and animal research. Evidence that diet influences blood cholesterol and CHD was reviewed by Grundy et al. in 1982.⁵ Dietary intervention trials uniformly report a positive trend toward decreased CHD risk with diets that lowered serum cholesterol levels. Mortality from CHD was decreased in most of

these trials. Furthermore, it is well established from metabolic and clinical studies that saturated fatty acids (and, in many people, excessive dietary cholesterol) raise blood total and LDL-cholesterol, and that total and LDL-cholesterol contribute directly to atherosclerosis and CHD. The Coronary Primary Prevention Trial showed that the cholesterol-lowering drug cholestyramine reduced LDL-cholesterol levels and incidence of CHD.⁶ Recently, in the Cholesterol Lowering Atherosclerosis Study,⁷ blood cholesterol levels were reduced through treatment with a combination of diet, colestipol and nicotinic acid. In summary, there is strong evidence for prevention of coronary heart disease through the reduction of high blood cholesterol levels by intervention with diet and/or drug.

National Cholesterol Education Program

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) initiated the National Cholesterol Education Program (NCEP) in 1985. The goal of the Program is to reduce illness and death from CHD by reducing high blood cholesterol. Educational efforts targeted at health professionals and the public aim to raise awareness and understanding about high blood cholesterol as a risk factor for CHD and the benefits of lowering cholesterol levels as a means of preventing CHD.

In 1987, the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, also known as the Adult Treatment Panel (ATP), presented its report, on the detection, evaluation and treatment of high blood cholesterol.^{8, 9} The ATP recommendations establish criteria to define persons who need medical intervention and provide advice on how to detect, set goals for, treat and monitor these patients. The target audience for the recommendations includes health

*Contemporary Nutrition Vol. 13, No. 1, 1988. Reprinted with permission from General Mills, Inc. Minneapolis, Minnesota.

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professionals, e.g., physicians, nurses, dietitians, pharmacists and others involved in the treatment of high blood cholesterol.

Identifying Persons at Risk

Serum total cholesterol should be measured least once every five years. Adults should also be evaluated for the presence of other CHD risk factors, including hypertension, cigarette smoking, diabetes mellitus, obesity and a history of CHD or of premature CHD in family members.

Levels of serum cholesterol below 200 mg/dl are classified as "desirable blood cholesterol," those 200 to 239 mg/dl as "borderline-high blood cholesterol," and those 240 mg/dl and above as "high blood cholesterol." This classification is based on at least two cholesterol measurements. If the second measurement obtained within one to eight weeks of the first measurement is within 30 mg/dl of the first measurement, the average of the two values can be used. Otherwise, a third test should be obtained within one to eight weeks and the average of the three tests used.

Patients with high blood cholesterol (>240 mg/dl) should repeat the test and have a further lipoprotein

analysis, as should those with borderline-high blood cholesterol (200-239 mg/dl) at high risk because they have definite (CHD or two other CHD risk factors). Lipoprotein analysis should include measurement of high-density lipoprotein (HDL) cholesterol, total triglycerides (TG), and an estimate of low-density lipoprotein (LDL) cholesterol.

Deciding to Treat

Selection of persons for cholesterol-lowering therapy should be based primarily on the LDL, rather than the total cholesterol level. Those with an LDL-cholesterol at or above 160 mg/dl are classified as "high risk LDL-cholesterol," and those of 130-159 mg/dl as "borderline-high risk LDL-cholesterol." Patients with high risk LDL-cholesterol levels, and those with borderline-high risk LDL-cholesterol who have definite CHD or two other risk factors, should begin treatment after a complete clinical evaluation, including the following laboratory tests: urinalysis, complete blood count and serum thyroid-stimulating hormone (TSH), glucose, alkaline phosphatase and albumin, in order to rule out the possibility of hypercholesterolemia occurring as a result of other metabolic disease.

Initial Classification and Recommended Follow-up Based on Total Cholesterol	
A. Classification*	
<200 mg/dl	Desirable Blood Cholesterol
200-239 mg/dl	Borderline-High Blood Cholesterol
≥ 240 mg/dl	High Blood Cholesterol
B. Recommended Follow-up	
Total Cholesterol <200 mg/dl	Repeat check-up examination within 5 years
Total Cholesterol 200-239 mg/dl	
Without definite CHD or two other CHD risk factors (one of which can be male sex)	Provide dietary information and recheck annually
With definite CHD or two other CHD risk factors (one of which can be male sex)	Lipoprotein analysis; further action based on LDL- cholesterol level
Total Cholesterol ≥ 240 mg/dl	Lipoprotein analysis; further action based on LDL- cholesterol level
*Based on the average of two cholesterol measurements that have been made within a 7-8 week time frame and provided that the range between the two tests does not exceed 30 mg/dl.	

Classification and Treatment Decisions Based on LDL-Cholesterol		
A. LDL-Cholesterol Values for Risk	Classification	
<130 mg/dl	Desirable LDL-Cholesterol	
130-159 mg/dl	Borderline-High Risk LDL-Cholesterol	
≥ 160 mg/dl	High Risk LDL-Cholesterol	
B. LDL-Cholesterol to Initiate Treatment and Minimal Goal	Dietary Treatment	
Risk Factor Status	Initiation Level	Minimal Goal
Without CHD or two other risk factors*	≥ 160 mg/dl	<160 mg/dl**
With CHD or two other risk factors*	≥ 130 mg/dl	<130 mg/dl***
	Drug Treatment	
Without CHD or two other risk factors*	≥ 190 mg/dl	<160 mg/dl
With CHD or two other risk factors*	≥ 160 mg/dl	<130 mg/dl
*LDL initiation level and goal is lower in presence of definite CHD or any two CHD risk factors. **Roughly equivalent to total cholesterol <240 mg/dl. ***Roughly equivalent to <200 mg/dl treatment.		

Dietary Treatment

Dietary modification is the primary approach to treating patients with high blood cholesterol. The minimal goals of therapy are to lower total and LDL cholesterol to levels below the cutpoints for initiating therapy, e.g., for high-cholesterol patients, serum cholesterol to below 240 mg/dl, LDL-cholesterol less than 160 mg/dl; for borderline patients, serum cholesterol to below 200 mg/dl, LDL-cholesterol less than 130 mg/dl. While LDL-cholesterol determination is recommended to select candidates for therapy, follow-up may be conducted with total cholesterol measurements, which are more convenient and less expensive. Any requirement for change in therapy, however, should be justified by LDL-cholesterol levels.

Dietary therapy is designed in two steps. Step-One Diet involves an intake of total fat less than 30% of calories, saturated fatty acids less than 10% of calories, and cholesterol less than 300 mg/day. Step Two Diet is a further reduction in saturated fatty acids to less than 7% of calories and in cholesterol to less than 200 mg/day. The major dietary influence on blood cholesterol level is saturated fat intake. To a lesser degree, substituting unsaturated fat facilitates reduction of blood cholesterol level. However, reduction in total fat intake *per se* does not lower blood cholesterol. Current fat intake is about 37% of calories. The recommendation to achieve a fat intake of less than 30% of calories is primarily a method to reduce saturated fatty acids as well as excess calories from fat. Both Diets recommend 30% of calories from fat.

The Nutrition Committee of the American Heart Association (AHA) has endorsed the Step-One and Step-Two approach to dietary change and will recommend it as dietary for hypercholesterolemia in place of its previous three-phased plan.¹⁰

Many patients will achieve an adequate blood cholesterol lowering with the Step-One Diet. Once this dietary pattern has been implemented, the serum total cholesterol level should be measured and adherence to diet assessed at 4 to 6 weeks and at 3 months. Cholesterol lowering of about 10%-15% should be expected during this period. If the cholesterol goal has not been met, then more intensive counseling and/or a further reduction in saturated fatty acid intake, e.g., the Step-Two Diet, may be needed.

A registered dietitian, experienced in counseling patients with high blood cholesterol, will be able to facilitate dietary adherence. Many health professionals, as well as consumers, can recite the general concepts of eating to lower blood cholesterol levels, e.g., eat less saturated fat and cholesterol and replace some of the saturated fatty acids with unsaturated fatty acids. The dilemma occurs in translating broad concepts into food choices in the supermarket and restaurant and in adapting recipes and menus. This practical knowledge is available from the experienced registered dietitian who has had academic training in food biochemistry and composition, as well as the principles of lipid metabolism and dietary response to food and nutrient intake.

Additional information may be obtained from the NHLBI and the AHA.

Drug Therapy

A minimum of three to six months of intensive dietary therapy and counseling should usually be completed before drug therapy is initiated. Drug therapy should be added to diet therapy, not substituted for it.

The decision to prescribe drug therapy should be made only after a sufficient period of strict adherence to dietary change has not proven adequate. For each patient, the degree of dietary change and the cholesterol response will determine the amount of medication required. No all patients can achieve desirable serum cholesterol and LDL-cholesterol levels even with optimal diet, but *less medication will be required with diet than without it. Thus one can reduce the potential side effects of the drug as well as the cost.*

For many patients, the use of one or two drugs usually provides an adequate LDL-cholesterol-lowering effect. The combination of a bile acid sequestrant with either nicotinic acid or an HMG-CoA reductase inhibitor has the potential of lowering LDL-cholesterol levels by 40%-50%. The combination of colestipol and nicotinic acid has been shown to have a beneficial influence on coronary atherosclerotic lesions.

After the initiation of drug therapy, the LDL-cholesterol level should be measured at 4 to 6 weeks, and then again at 3 months. When the response to drug therapy has been adequate, then the patient's cholesterol levels should be monitored about every four months. Where it is apparent that the cholesterol response is stable, long-term monitoring of both cholesterol and LDL-cholesterol can be conducted at annual follow-up visits. It is important that the patient understand that when both dietary and drug therapy have been shown to be necessary, they are likely to be needed for a lifetime.

Future Efforts of the NCEP

Additional panels of the NCEP are planned. A Population-Based Panel will examine the issue of shifting the distribution of blood cholesterol levels in the population to a lower range. The Treatment Panel on children and adolescents will address specific issue of diet/drug intervention in children with high blood cholesterol. The NCEP also has initiated a public education campaign to increase public awareness of the dangers of high blood cholesterol, the importance of having levels checked and the significance of those levels.

Summary

Recommendations of the National Cholesterol Education Program-Adult Treatment Panel establish criteria that define adults with high blood cholesterol who will benefit from medical intervention and provide guidelines on how to detect, establish goals, treat and follow these patients over time. These criteria, which categorize cholesterol levels of over 240 mg/dl as "high" and those

below 200 mg/dl as "desirable," define a large group of American adults who should be screened, identified and treated in order to prevent the development of coronary heart disease. It is estimated that one out of four adults, or about 40 million Americans, have blood cholesterol levels that are high enough to warrant further evaluation and possible medical intervention.

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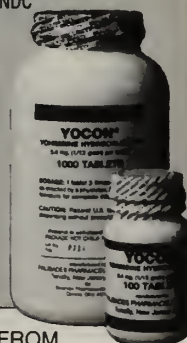
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CARTAS AL EDITOR

The Problem of Heart Disease in Puerto Rico

It is well known that heart disease is the leading cause of death in our island: 25 percent of all deaths are due to heart disease, with coronary artery disease (CAD) being responsible for more than 60% of all the heart disease related deaths.¹ The most recently published statistics demonstrate higher mortality rates for both chronic and acute heart diseases in Medicare patients in Puerto Rico than in the U.S.² Myocardial revascularization by surgical (bypass) or interventional cardiologic maneuvers (angioplasty) are the most effective therapeutic approaches to significant CAD; coronary artery surgery has been proven to prolong life in addition to markedly improving quality of life in a large subset of patients with CAD and impaired left ventricular function. The only reason to submit a patient for cardiac catheterization and coronary arteriography is to investigate the possibilities of myocardial revascularization by one of the above mentioned techniques, the diagnosis of CAD is made by clinical and noninvasive methods. Therefore, cardiologists practicing catheterization and coronary angiography must be ready to react immediately to the findings of these invasive diagnostic techniques: ready to proceed with angioplasty if indicated, and ready to send the patient for surgery if this is deemed necessary. However, only 3 of the 8 cardiac catheterization laboratories currently operating in Puerto Rico are prepared to function under these terms. The currently common practice of referring patients found to have correctable heart disease in our catheterization laboratories to the U.S. for treatment is biased by necessity: only those patients with the most stable problems are capable of surviving the required waiting period to be referred elsewhere, while the sickest patients have to be treated on the island. Perhaps this could explain the fact that the mortality rates for our Medicare patients with heart disease are significantly higher here than in the U.S., and also play an important role in the high death rate of heart disease in the island. It is time for our medical community and hospital directors and administrators to look at these facts and put them in the proper perspective. No progress will be made against the number one killer in our society unless basic scientific principles that have been proven to work effectively in other countries are applied here with strict controls of quality and common medical sense.

Manuel E. Lores-Suárez, MD, FCCP
Rafael A. Brito-Arache, MD, FACS

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REPORT: COMMON MISCONCEPTIONS LEAD TO IMPROPER CARE OF GUNSHOT WOUNDS

Major misconception in the field of wound ballistics often lead to improper treatment of gunshot wounds, suggests a report in the *Journal of the American Medical Association*.

"Gunshot wounds are a fact of life in our society," says the author, Martin L. Fackler, MD, of the Letterman Army Institute of Research, Presidio of San Francisco, Calif. "However, the assumption that military conflicts, wound ballistics research, and daily hospital experience in our larger cities have provided the knowledge and skill to ensure proper treatment of these injuries is far from correct."

Fackler, who conducts wound ballistics studies at the research institute, has reviewed existing scientific literature on the effects of gunshots. Much of this literature is based upon unscientific notions about how bullets and living tissue interact, he says. "Widespread dogma claims that high-velocity projectiles cause wounds that must be treated by extensive excision of tissue around the missile path, whereas those caused by low-velocity missiles need little or no treatment." This dogma has led to unnecessary debridement of wounds from high velocity bullets while low-velocity projectile wounds are dangerously undertreated, he says.

These misconceptions are nurtured by two half-truths concerning cavitation, the temporary displacement of tissue which follows the path of a fast moving projectile. One half-truth is that cavitation requires extensive tissue excision. Unlike tissue directly in the way of the bullet, which gets crushed, tissues in the temporary cavity caused by a high speed projectile are stretched and may not necessarily suffer lasting harm. The other is that high-velocity missiles cause cavitation while slower moving projectiles do not, the author writes.

"Elastic tissues such as the bowel wall, the lung, and muscle are relatively resistant to damage from such stretching, while solid organs such as the liver are not,"

the author says. "Most muscle stretched by temporary cavitation survives; this survival has been verified in every case in which muscle was allowed to remain in situ and healing was followed to completion."

Fackler, who says that ballistic tests clearly show that many large, low velocity bullets also produce extensive cavitation, blames much of the current misconception on the high-speed movie camera, which "shifted emphasis in wound ballistics from scientific method to spectacular cinematography. This shift so distorted and exaggerated the concept of temporary cavitation that, to some, it came to represent the entirety of the projectile tissue interaction."

The author also attributes the misconceptions to anecdotal reports and misinterpreted war trauma experience. "Rarely are weapon characteristics and the absence of intermediate targets known with certainty on the battlefield. Memory mixes all types of war wounds together, assumptions on treatment efficacy are made despite lack of follow-up information, and statements about treatment rendered in the field of action are frequently inaccurate."

In treating gunshot injuries, Fackler says, they physician should make an objective evaluation of the wound with X-rays and other means, and not base treatment upon characteristics of the bullet, which patient, witnesses or police may claim caused the wound. Statements about the weapon used are anecdotal, frequently wrong, and almost always prejudicial for assessing the nature of the wound, he writes. "As in the treatment of any other form of trauma, objective data should guide treatment decisions," he concludes.

JAMA May 13, 1988

WALKING FOR HEALTH AND FITNESS

A report in the *Journal of the American Medical Association* backs walking as a form of exercise that may have a number of highly beneficial health effects. Various studies have linked regular physical activity—even low- and moderate-intensity exercise like walking—with "important cardiovascular health benefits" and reduced risk of coronary artery disease, says the report by James M. Rippe, MD, of the University of Massachusetts Medical School, Worcester, and colleagues. Walking has been shown to reduce anxiety and aid in weight loss, they say, and may also help to improve the cholesterol profile, control hypertension, and slow the process of osteoporosis. Recent studies suggest brisk walking provides strenuous enough exercise for cardiovascular training in most adults, they add. "Walking provides an effective form of activity to help patients establish the kind of consistent, lifelong exercise programs that have been shown to carry the most important long-term health benefits," they conclude. *JAMA May 13, 1988*

TREATMENT OF COMMON TYPE OF FISH POISONING

A common osmotic-type diuretic called mannitol may be effective in treating acute ciguatera fish poisoning, the most frequently reported seafood-related disease in the United States, a report in the *Journal of the American Medical Association* suggests. This poisoning, caused by a common fish toxin endemic in the Caribbean and Indo-Pacific Islands, has a reported annual incidence of 100 to 300 per 100,000, says the report by Neal A. Palafox, MD, of the Armer Ishoda Memorial Hospital, Majuro, Marshall Islands, and colleagues. The toxin is passed through the food chain and concentrated in certain fish. Eating affected fish, cooked, frozen or raw, may cause poisoning. The authors used intravenous mannitol to treat 24 patients with this fish poisoning, and say each patient's condition "improved dramatically." Although noting that their study was uncontrolled and the mechanism of the drug's action unclear, the authors still say mannitol "should be considered for initial use in patients with significant clinical signs or symptoms of ciguatera fish poisoning."

JAMA May 13, 1988

ULTRASOUND IN PROSTATE CANCER

Transrectal ultrasound imaging is a safe means of screening for early prostate cancer and staging such cancers once found, but its effectiveness in screening and staging, remains unproven, an AMA science study panel says in the *Journal of the American Medical Association*. Seventeen of the 24 Diagnostic and Therapeutic Technology Assessment (DATTA) panelists consider the technique safe for screening asymptomatic patients for early prostate cancer, and 20 find it safe in staging. But when asked about effectiveness, 18 panelists called the technique investigational or indeterminate in screening; 14 held the same view in staging. "A major problem is the lack of agreement on the identifying characteristics of carcinoma in ultrasound images of the prostate," the report says. "In addition, the inability to visualize the pelvic nodes via transrectal ultrasound inherently limits its utility for staging." Still, the report adds, the panelists and the literature indicate "transrectal ultrasound may well have a significant role to play in the future treatment of prostatic cancers."

JAMA May 13, 1988

KIDNEY/PANCREAS TRANSPLANTS IN DIABETICS

A study in May's *Archives of Surgery* reports significant success in combined kidney/pancreas transplants in insulin-dependent diabetics, and suggests such

surgery be considered earlier in the course of the disease. A. Benedict Cosimi, MD, of Massachusetts General Hospital, Boston, and colleagues performed simultaneous kidney/pancreas transplants in 12 diabetics with such advanced secondary complications as blindness, vascular disease and nerve damage. Blood glucose levels promptly returned to normal in all 12. Two of the 12 later died, but a year's follow-up, the others remained independent of insulin and dialysis (kidney damage is common in diabetes). "The success of pancreas transplantation in diabetics with advanced complications now approaches that of other organ allografts," the authors say. "It therefore appears reasonable to recommend transplantation for diabetics with less severe secondary complications, since these candidates are most likely to realize the potential benefits of long-term (normal blood glucose levels)."

NEW DRUG SHOWS PROMISE IN PANIC ATTACKS

A new derivative of benzodiazepines (a class of drugs including Valium) shows promise in treating panic attacks and panic disorder, a major study in May's *Archives of General Psychiatry* reports. James C. Ballenger, MD, of the Medical University of South Carolina, Charleston, and colleagues at seven centers in the United States, Canada and Australia, say the drug, alprazolam, "was found to be effective and well-tolerated" in patients with panic attacks and disorder. The first phase of the two-phase study, sponsored by the Upjohn Co., looked at the effects of alprazolam versus placebo in more than 500 patients over eight weeks. After four weeks, 82 percent of the drug-treated group were rated "moderately improved or better" compared with 43 percent of the placebo group. At that point, half the drug group was free of panic attacks, versus 28 percent of the placebo group. The authors caution that "further controlled trials are needed to determine the proper dose of alprazolam, optimal length of treatment, and comparative efficacy and side effects with other effective medications." The larger, second phase of the study, yet to be published, compares the effects of alprazolam, the commonly used panic attack drug imipramine, and placebo.

DOCTORS URGED TO USE VARIETY OF TECHNIQUES TO HELP SMOKERS QUIT

The techniques used to help smokers quit don't appear to matter as much as the amount and variety of personalized advice and support patients receive from physicians in helping them kick the habit, concludes a study in the *Journal of the American Medical Association*.

The U.S. Preventive Services Task Force study found "little reason for confidence in the scientific validity of

claims that any particular intervention strategy is uniformly more effective than firm, consistent, and repeated help and advice to stop smoking," say authors Thomas E. Kottke, MD, MSPH, of the Mayo Clinic, Rochester, Minn., and colleagues. "Success was not associated with novel or unusual interventions. It was the product of personalized smoking cessation advice and assistance, repeated in different forms by several sources over the longest feasible period."

A related study in the same *JAMA* issue reports that the antihypertensive drug clonidine may help smokers to quit by reducing their craving for cigarettes. Clonidine, which inhibits sympathetic nervous system activity, previously has been shown to reduce opiate and alcohol withdrawal symptoms.

The report by the Task Force, a government-coordinated research group that studies public health problems and recommends remedial policies, analyzed the results of 39 controlled smoking intervention trials. These involved many different and some unusual strategies to aid doctors in helping their patients stop smoking, including acupuncture, behavioral modification, sensory deprivation, substituting nicotine gum for cigarettes, and providing information about smoking and health, and advice about quitting. "However, the results reported in smoking cessation trials vary widely and with little apparent consistency," the authors say.

The most effective interventions employed more than one modality for motivating behavioral change, involved both doctors and non-doctors in an individualized face-to-face effort, and provided the motivational message on multiple occasions over the longest possible time period. The authors conclude that developing and instituting the most fruitful smoking cessation programs probably require a focus on how the nonsmoking message can be given clearly, repeatedly, and consistently through every feasible delivery system. Based on this study, the Task Force recommends "patients should be exposed to a variety of intervention techniques on multiple occasions, delivered by physicians and non-physicians."

An accompanying editorial calls for development of a coordinated national strategy for expanding physicians' participation in the campaign for a smoke-free society. "Unfortunately, data suggest that physicians as a group may not be doing all that they could to encourage cessation among patients who smoke," says the author, Ronald M. Davis, MD, of the Centers for Disease Control, Rockville, Md. In addition, Davis expresses concern that lack of coordination among organizations may be causing counterproductive duplication of effort.

"Clearly, the vast power of the medical profession to curb the use of tobacco has not been fully tapped," he says. "Medical societies, voluntary health organizations, public health agencies, and other interested parties need to better coordinate their activities to mobilize a medical assault on smoking. Collectively, these groups should examine how scarce resources should be apportioned to accomplish this goal."

In a related report, Alexander H. Glassman, MD, of Columbia University and the New York State Psychiatric Institute, and colleagues, studied clonidine as a potential smoking cessation aid in 71 heavy smokers enrolled in a

four-week placebo-controlled trial. The drug was given to a random sample of heavy smokers who had made at least one previous effort to quit. The success rate for smokers taking clonidine was more than twice the rate for a placebo-treated group of smokers. After six months, cessation rates remained significantly higher among the clonidine group.

Clonidine's beneficial effect was far stronger in women studied than in men, who showed no cessation benefit from the drug, the authors say. Another surprising result was the unexpectedly high prevalence (61 percent) of a history of depression in the smokers studied. A history of depression predicted cessation failure, say the authors of the study, which was supported by grants from Capital Cities Communications, Inc., the Boehringer Ingelheim Corp. (the drug's manufacturer), and the New York State Health Research Council.

Commenting editorially, John R. Hughes, MD, of the University of Vermont, Burlington, says this evidence of the first non-nicotine drug that can effectively aid smoking cessation is exciting, but preliminary. The six-month follow-up cessation rates with clonidine are similar to those obtained with nicotine gum, he says, but unlike nicotine gum, which appears to suppress withdrawal symptoms, clonidine seems to work by reducing the craving to smoke. He also acknowledges an advantage of clonidine treatment, that it does not continue to expose the patient to nicotine, which "may have harmful effects and may prolong dependence."

JAMA May 20, 1988

EVEN LOW-LEVEL SMOKING MAY REDUCE HDL LEVELS: STUDY

Even short-term, low-level smoking may help lead to cardiovascular disease by affecting blood levels of a heart-protecting lipoprotein, suggests a study in the *Journal of the American Medical Association*.

The study's authors, James H. Dwyer, PhD, of the Institute for Health Promotion and Disease Prevention Research, University of Southern California School of Medicine, Pasadena, and colleagues in Germany and Switzerland, examined data collected from school children, aged 12 to 14, in Berlin and Bremen, Germany. They measured blood levels of high-density lipoprotein cholesterol (HDL-C) in children before they began to smoke. These were compared with HDL-C levels in these children after they became light (one to 39 cigarettes per week) or moderate (more than 40 per week) smokers, and with those of children who didn't smoke.

HDL-C is believed to play an important role in preventing cardiovascular disease. No differences in baseline HDL-C levels were found between children who later took up smoking and those who didn't showing that the smokers were not characterized by lower HDL-C levels before starting to smoke. Nevertheless, a dose-related decrease in HDL-C levels was later found in the children who smoked, compared with those who didn't.

The authors say their finding "that the earliest stages of smoking in youth are associated with a more atherogenic profile of serum lipoproteins suggests that adverse vascular effects of smoking could commence in these earliest stages and accumulate," and that this challenges the view that smokers' higher cardiovascular disease risk is due primarily to short-term effects. "Within this context of present knowledge, the current finding of a more atherogenic lipid profile among new smokers emphasizes the importance of primary prevention. Exposure to even low concentrations of cigarette smoke for relatively short periods of time may contribute to vascular damage that is difficult to reverse," they conclude.

JAMA May 20, 1988

STUDY: BREAST CANCER-ALCOHOL LINK A WEAK ASSOCIATION

Although an association between alcohol consumption and breast cancer can't be completely ruled out, evidence suggests any such link is weak at best, concludes a study in the *Journal of the American Medical Association*. It proposes that socioeconomic factors correlated with moderate or social drinking may be responsible for the elevated breast cancer risk seen in some studies.

A total of 14 studies now have focused on alcohol as a potential risk factor in breast cancer, says the report by Randall E. Harris, PhD, MD, and Ernst L. Wynder, MD, of the American Health Foundation (AHF), New York City. Ten of these have shown a "weak positive association" and four others (including the new study) have reported either no effect or even slight negative effects.

In their study, Harris and Wynder examined 1,467 cases of women with breast cancer, and nearly 10,178 sex- and age-matched hospital controls, for alcohol consumption and other potential breast cancer risk factors. Study subjects were drawn from a large computerized medical data registry compiled by the AHF and representing patients from 20 hospitals in major U.S. cities.

After figuring odds ratios to assess the effects of risk factors and adjusting for confounding variables, the researchers could find "no evidence that alcohol has a role in the genesis of breast cancer." One group studied, a subgroup of thin women, did have higher, unadjusted breast cancer risks associated with drinking various amounts of alcohol daily. However, the authors note, the pattern "is not consistent with a dose response"; that is, the risk did not increase with increasing consumption. In addition, they report, when the odds were adjusted for a risk profile of confounding factors, including education and occupation (strong correlates of age at first pregnancy and birth of first child), the risk estimates dropped to levels not statistically significant from on increased risk.

Various socioeconomic factors were found to influence alcohol consumption, including age, religion, education, marital status, body mass, and cigarette smoking. Such social factors "could have an impact on or be confounded with a woman's reproductive history, which in turn may

condition her breast cancer risk."

"Given the interdependence of socioeconomic and physiological determinants of social drinking and their potential influence on reproductive history, it would appear difficult to exclude the possibility that cofounders and their interactions are responsible for the increased breast cancer risk associated with social drinking (two to three drinks per week)," the authors write.

"In view of the largely negative findings of our study, we cannot at this point regard alcohol intake to be causatively related to breast cancer development," they conclude. "Therefore, any recommendations to a public already concerned about the many agents established to cause cancer should not suggest that stopping social drinking can modify breast cancer risk.

"Epidemiologists need to examine the issue at hand further to determine definitively whether the association found by some investigators between moderate alcohol intake and breast cancer is real, or whether we are dealing with a web of confounders with social status at its center."

JAMA, May 20, 1988

ORAL ACYCLOVIR FOR HERPES SIMPLEX PROCTITIS

Oral acyclovir therapy can alleviate some of the clinical signs of rectal herpes simplex virus (HSV) infection, the most common cause of non-gonococcal proctitis in homosexual men, concludes a report in the *Journal of the American Medical Association*. The report, by Ann M. Rompalo, MD, of the University of Washington, Seattle, and colleagues, involved a double-blind study of 2 grams daily versus placebo in 29 homosexual men with rectal HSV infection. After three days of therapy, 80 percent of the drug-treated group no longer had HSV isolated from their rectal lesions, compared with 25 percent of placebo recipients, says the study, which was supported by the Burroughs-Wellcome Co., Research Triangle Park, NC. The average duration of lesions also was significantly shorter in the drug group. In addition, duration of local signs and symptoms of proctitis was shorter in the acyclovir recipients than in the placebo group, although the differences were not statistically significant, the authors report.

JAMA May 20, 1988

IS TOPICAL TRETINOIN TERATOGENIC?

It is well-documented that tretinoin, or retinoic acid, a Vitamin A-derivative used to treat acne, can have teratogenic effects—that is, the ability to cause fetal deformities. The *Questions and Answers* section of the *Journal of the American Medical Association* looks at whether tretinoin is teratogenic if used *topically* by women during pregnancy. Albert M. Kligman, MD, PhD, of the University of Pennsylvania School of

Medicine, Philadelphia, who has studied Vitamin A derivatives and their dermatologic effects for years, says there is no evidence that tretinoin presents a risk of birth defects when used topically. The concentration used, 0.1 to 0.5 percent, is low, and the drug is rapidly metabolized by the skin, he writes. "I estimate the risk (of teratogenicity in topical use) to be zero," he says. "No cases have been reported after nearly 20 years of use by millions of patients with acne."

JAMA May 20, 1988

HEAVY MATERNAL EXERCISE MAY SLOW FETAL HEART RATE: STUDY

Very vigorous maternal exertion during pregnancy may result in a slowing of fetal heart rate, raising concerns about inadequate fetal oxygen exchange, but less intense exercise doesn't appear to have such an effect, a report in the *Journal of the American Medical Association* concludes.

The significance of such fetal bradycardia is as yet unknown, note the study's authors, Marshall W. Carpenter, MD, of Women's and Infants Hospital, Providence, R.I., and colleagues. Still, they recommend that pregnant women limit vigorous exercise to activities requiring heart rates of 150 beats per minute or less.

Doppler monitoring of fetal heart rates during maternal exertion has suggested that fetal bradycardia occurs often during vigorous exercise, raising concerns about fetal safety, the authors write. But obtaining an accurate fetal heart rate reading using this technique is difficult because of interference caused by the motion of the exercising woman, they say. As a result, the authors used a different technique, two-dimensional ultrasonic imaging, which "appears to be accurate and reliable" in measuring fetal heart rate, they say.

The authors studied 45 pregnant women, average age 29 years, who exercised briefly at maximal (maximum aerobic capacity, or oxygen uptake, and heart rate) and submaximal levels on an exercise cycle. All of the women had uncomplicated pregnancies; 21 reported exercising vigorously more than once a week prior to pregnancy, and 16 said they engaged in regular exercise during pregnancy.

Average fetal heart rate did not change during exercise, they study says, although there was one episode of fetal bradycardia during a submaximal exertion test. However, 16 episodes of fetal bradycardia were noted within three minutes after the women finished exercising; 15 of these followed maximal maternal exertion.

The observation of fetal bradycardia raises concerns about the possibility of insufficient fetal oxygen exchange, the authors say. Although not actually measured in the study, the homeostatic mechanisms maintaining fetal oxygen extraction might be compromised by "the combined effects of reduced uterine perfusion (blood flow) during vigorous exertion and the decrease in cardiac output after exercise," they say. But, they note, "we assume that possible fetal hypoxia after

maternal exercise is mild and transient, since all fetuses had normal nonstress test results within 30 minutes of exercise cessation."

Fetal bradycardia after maximal maternal exercise during the study "did not predict future perinatal problems" for the study subjects, the authors note. Three infants involved in the study as fetuses died within five weeks of birth, but "none of these infants demonstrated fetal bradycardia during this study." One of the three infants was born with an infection, one had a brain tumor and one died of sudden infant death syndrome, they note.

"In our study, we found the mean fetal cardiac rate to be stable during and after maternal exertion and independent of exercise intensity," the authors conclude. "Our findings suggest that unexplained fetal bradycardia during maternal exertion of any intensity is rare. Similarly, fetal bradycardia was rarely observed after (submaximal) maternal exercise..."

"Maternal exertion approaching maximal aerobic capacity, however, may be followed by fetal bradycardia," the authors write. "The significance of this bradycardia is, as of yet, unknown. However, it seems prudent to recommend that pregnant women limit their vigorous exercise to activities requiring heart rates of 150 beats per minute or less and conclude with a gentle and continuous slowing of effort during recovery."

The researchers acknowledge that the exercise periods in their study were brief, "so we cannot comment on the effect of exercise duration on the fetal heart rate response."

JAMA May 27, 1988

COMMENTARY: ANTI-AIDS MEASURES MUST TARGET INFECTED CELLS

Antiviral drugs and vaccines to prevent transmission of human immunodeficiency virus (HIV) must be aimed at attacking HIV-infected cells, not just the virus, says a commentary in the *Journal of the American Medical Association*.

Current approaches to prevent the transmission of the AIDS-causing virus are focused on the retrovirus alone, says the author, Jay A. Levy, MD, of the University of California School of Medicine, San Francisco. However, biologic and epidemiologic studies indicate that cell-free virus in body fluids is unlikely to be a meaningful source of HIV transmission. Researchers' attention should be on the role of virus-infected cells in the spread of AIDS, he says.

Levy bases his opinion on studies conducted in his and other laboratories that have found only very low amounts of virus outside of cells in blood serum, semen, urine, tears, saliva and vaginal secretions. Numerous researchers have demonstrated the presence of HIV not only in T lymphocytes but in macrophages (scavenger) and other white blood cells that may serve as reservoirs and factories for continual virus production and as transmitters of the disease, he says.

"Normal seminal fluid contains an average of 3 million white blood cells per milliliter," Levy reports. This number can be much higher for individuals concurrently infected with sexually transmitted diseases or prostatitis. Based on the author's cell-culture studies, he believes that HIV-infected white blood cells in semen may play a major role in transmitting AIDS. The mechanism of transmission may involve cell-to-cell contact between the infected white blood cells from an infected person's semen and the mucosal cells or white blood cells of his sexual partner. Such transmission would be greatly aided by the presence of lesions from venereal infections, such as chancroid or herpes simplex, he says.

The author believes the very low incidence of transmission from infected women to men may be due to "the limited quantities of virus and virus-infected cells present in vaginal/cervical fluid. Furthermore, breaks or abrasions in the penile and urethral epithelium or the mucosal inner layer of the foreskin of the male partner probably need to be present to permit HIV infection." The author notes that lack of circumcision carries an increased risk of infection for men in Africa, and that in Africa—where heterosexual spread is prominent—transmission appears to be enhanced by concurrent venereal diseases that cause ulcerations in both men and women.

As additional evidence that infected cells may be the major means of HIV infection, Levy reports that "bovine leukemia and human T-cell leukemia virus are transmitted primarily by the infected cell. Visna in sheep is passed almost exclusively by infected macrophages."

"Unlike strategies to fight other human viruses, such as measles virus, poliovirus, and hepatitis virus, blocking free-virus entry into the host without removal of the infected cell would not lead to effective prevention. The control and cure of AIDS will result only when the infected cell itself is eliminated. Antiviral drugs and vaccination to prevent infection with HIV must induce the production of immune *cytotoxic* responses acting against the infected cell," he concludes.

JAMA May 27, 1988

HIGH-DOSE EPINEPHRINE FOR CARDIAC ARREST

A report in the *Journal of the American Medical Association* describes two cases in which high-dose epinephrine (adrenalin) therapy—six and 10 times the generally recommended dosage—was used successfully to resuscitate patients in cardiac arrest. Eric M. Koscove, MD, of the Los Angeles County-University of Southern California Medical Center, Los Angeles, and Norman A. Paradis, MD, now with Henry Ford Hospital, Detroit, say the high-dose epinephrine was used when standard therapy failed to restore regular heart rhythms in the two patients. In both cases, there was a return of spontaneous circulation after administration of epinephrine. One patient, a 71-year-old man, later

died, but the other, a 59-year-old woman, recovered. "Recent studies suggest that presently recommended epinephrine doses may be too low, and investigation of graded epinephrine doses for the treatment of cardiac arrest is indicated," the authors say.

JAMA May 27, 1988

COCAINE-CAUSED SUICIDE?

Suicide by cocaine overdose may be a problem of unrecognized proportion, says a letter in the *Journal of the American Medical Association*. Author Kris Sperry, MD, of the University of New Mexico School of Medicine, Albuquerque, describes two deaths from intentional intravenous cocaine use studied by New Mexico officials in the past two years. In both cases, involving a 25-year-old college student and a 33-year-old construction worker, "notes at the scene indicated that the primary reason for suicide was addiction to cocaine... with despair brought about by the apparent inability to break the cycle of drug dependence," Sperry writes. Although the proliferation of cocaine abuse is known to cause a variety of health problems and deaths, "suicide with cocaine as the toxic agent has not yet, to my knowledge, been reported in the United States," Sperry writes. Although apparently uncommon, the problem may be "a heretofore unsuspected facet of the cocaine problem in this country," he says.

JAMA May 27, 1988

STUDY: BOWEN'S DISEASE NOT INTERNAL MALIGNANCY MARKER

Despite years of speculation to the contrary, Bowen's disease, a type of skin cancer that develops at various sites around the body, is not a skin marker for internal malignancy, says a Danish study in May's *Archives of Dermatology*. Flemming Reymann, MD, of the Finsen Institute, Copenhagen, and colleagues base the conclusion on a retrospective study of 581 Bowen's disease patients treated over a 40-year period. Patient records were traced to identify later cases of non-skin cancer. Fifty study subjects were found to have non-skin cancer—more than the expected number of 40, "but this difference was not significant," the authors say. In addition, they note, "this lack of association was equally true for (Bowen's disease) on sun-exposed and non-sun-exposed skin." But an accompanying editorial by Jeffrey P. Callen, MD, of the University of Louisville (Ky.) raises a number of concerns about the Danish report. Callen says a subtle bias that may have clouded previous studies of a Bowen's disease-internal cancer link "may have been minimized (in the new study), but it was not totally eliminated." As a result, he says, "the relationship of Bowen's disease to internal malignancy is still uncertain."

FOOD MAY HAVE BROADER ROLE IN ALLERGIC RHINITIS

Researchers apparently underestimate the role that foods have in triggering allergic rhinitis—nasal blockage accompanied by sneezing, itching and a runny nose—suggests a report in May's *Archives of Otolaryngology-Head and Neck Surgery*. Zdenek Pelikan, MD, of the Institute of Medical Sciences "De Klokkenberg," Breda, the Netherlands, looked at the link between food ingestion and nasal response in 142 patients suffering from perennial allergic rhinitis. These patients underwent a series of tests, including "ingestion challenges" with selected foods (sampling small amounts of cheese, chocolate, vegetables, fruits, nuts, meat, milk, yogurt, spices, and alcoholic beverages). Their nasal response to each was measured. Forty-seven patients with a "positive food allergy history" were tested, and 41 had a "positive nasal response" to 65 of 72 food ingestion challenges. But among the other 95 patients whose food allergy history was unknown, 54 had positive nasal responses to 68 of 132 food ingestion challenges. "It can be concluded that the involvement of foods in allergic rhinitis is more frequent than is usually expected," the authors say. However, they note, "the mechanisms underlying the nasal response to foods are not yet fully clarified."

"THE LURKING SPERM": A REVIEW OF VASECTOMIES THAT FAILED

Most surgeons who perform vasectomies, the common male sterilization procedure, acknowledge occasional failures, some of which cause unwanted pregnancies, says a report in the *Journal of the American Medical Association*.

The report by Philip M. Alderman, MD, whose practice in West Vancouver, British Columbia, is restricted to vasectomies and related research, reviews the failures seen in his own practice. From 1962 to 1986, Alderman performed 8,879 vasectomies using the most common surgical technique. In a subgroup of 5,331 men who returned for at least two postoperative semen tests, Alderman found 97 failures of all types, five of which were discovered as a result of pregnancy.

Although Alderman acknowledges controversy over the best vasectomy technique to use, he cites authors who have stated that the technique has nothing to do with vasectomy failures. "Failure is just one of several complications of vasectomy," he concludes.

But an accompanying editorial, by Stanwood S. Schmidt, MD, of the University of California, San Francisco, disagrees with this view, saying failure is not a complication from vasectomies performed with the proper technique. Schmidt, who uses a less common surgical technique, reports no failures in the more than 5,000 vasectomies he has performed over 30 years. Both patient and surgeon need to know when sterility can be considered permanent, he says. "An operation with an uncertain result is not a good operation."

In the common vasectomy procedure called vasoligation (used by Alderman), a section of the vas deferens—the duct carrying sperm from the testicles to the seminal vesicle, where they are stored until ejaculation—is removed and the ends tied closed with a surgical knot.

It has long been known that the vas deferens can regenerate over significant distances as long as its sheath is intact, says Schmidt, who uses a more involved procedure. He transects the vas deferens and cauterizes the ends to produce a plug of scar tissue, then pulls the sheath of the vas deferens down over the cauterized ends and ties it to form a seal against possible leaks. He believes sperm leakage can stimulate surrounding tissues to form canals that reconnect the ends of the vas deferens years after the patient was declared sterile.

After a vasectomy, patients are generally considered sterile if two semen samples at least four months after surgery and a month apart show no sperm, Alderman says. In his review, he found 32 "early overt failures"—patients for whom the post-vasectomy tests had shown significant numbers of sperm in their semen. In addition, there were four "late overt failure," which he discovered when patients returned for testing after their partners became pregnant. Although post-vasectomy tests had shown them to be sterile, retesting more than four years later revealed significant numbers of sperm in their semen.

Alderman also found 59 patients whose semen contained very small numbers of nonmotile spermatozoa after their vasectomies. The semen of two others, though free of sperm after surgery, were found years later to have small numbers of nonmotile sperm. Alderman calls these "technical failures," since, he says, they are highly unlikely to lead to pregnancy (one of the two was retested after his wife became pregnant, but it was not possible to confirm whether the patient was responsible for the pregnancy).

"Failures result either because one or more vasa deferentia are left uncut at surgery or because the continuity of the vas deferens was in some way restored following its interruption," he says. "An uncut vas deferens should result in an early and overt failure, but a recanalization may occur at any time and may be of any degree of patency or duration." Alderman recommends further research into the relationship between vasectomy technique and failure rate and other complications. "Whether other surgical techniques can produce improved failure rates consistently and in a reproducible manner remains to be determined," he concludes. But Schmidt disagrees, saying "technique has *everything* to do with failure. Most surgeons do not study this operation, even though its principles are simple and the widely used 'vasoligation' leads to failure."

JAMA June 3, 1988

FDA CAUTIONS PHYSICIANS ON ASPIRIN IN PREVENTING HEART ATTACK

Food and Drug Administration officials, writing in the *Journal of the American Medical Association*, underscore

the preliminary nature of a recent study suggesting aspirin use can prevent heart attacks, and urge physicians to exercise great care in patient selection for such therapy.

The report, by FDA Commissioner Frank E. Young, MD, PhD, and colleagues, says the need to consider the baseline risks of patients who might seek aspirin therapy for primary heart attack prevention has been underemphasized in lay press reports about the Physician's Health Study, preliminary results of which were published in the Jan. 28 *New England Journal of Medicine*. That ongoing study, involving 22,000 physicians, suggested healthy men taking an aspirin every other day can dramatically cut their risk of heart attack. Participants in the double-blind, placebo-controlled study also are testing whether taking beta carotene every other day can reduce the incidence of cancer.

"Given the preliminary nature of the published report, the lack of extensive critical scientific discussion of its findings, and the absence of authoritative professional labeling based on the study, physicians will, for a time, be forced to make their professional judgments about aspirin use on the basis of incomplete information," the FDA authors write. "At present, in the absence of additional data, the FDA is faced, in interpreting the study, with the same problems that the practitioner must face when confronted by a patient who has read about the preliminary findings of this study in the lay press."

The finding of the Physicians Health Study that has received the greatest attention was a "statistically impressive and clinically meaningful" reduction in both fatal and nonfatal heart attacks in study subjects who took a 325 mg aspirin every other day, the FDA authors say. However, they say, two other findings have received less notice: 1) Despite the significant reduction in heart attack deaths, overall cardiovascular mortality was identical in the aspirin and non-aspirin groups and, 2) There was an increase in the aspirin group of one type of stroke (hemorrhagic), "not an unexpected finding, given the effect of aspirin on platelet function."

"Even under the most positive assumptions regarding the conduct of the study and its results, proper interpretation is crucial to obtaining any potential benefits of aspirin therapy," the FDA paper says. "For example, if there is a 47 percent *reduction* in acute myocardial infarction and an *increase* in serious intracranial hemorrhage, whether a particular patient will gain or lose depends on his or her baseline risk for those events."

Although the study's authors and the editor of the *NEJM* have both rightly emphasized the preliminary nature of the Jan. 28 report and the need for careful patient selection in prescribing aspirin, "the need to consider baseline risks of patients has not been pointed out in most press reports about the study," FDA paper says. In addition, it notes, such reports "have not emphasized the special nature of the population studied or the special concern that arises when the study results are applied broadly, eg, to women as well as men."

The report says the FDA will review and evaluate the complete Physicians Health Study data, plus any pertinent data from a similar study of British physicians, before moving to develop authoritative labeling of

aspirin for professional use in primary heart attack prevention. Such labeling for over-the-counter drugs "is targeted specifically for the practitioner and does not appear on the consumer packaging," the authors say. The FDA has approved such labeling for aspirin with regard to reducing the risk of a second heart attack.

In the meantime, the paper says, an "emphasis on the need for careful patient selection is appropriate. It is the individual physician who knows the patient's baseline risk status and who, with the patient, can weigh the risks and benefits of aspirin treatment and other means of risk reduction."

JAMA June 3, 1988

RUBELLA ANTIBODIES PERSIST FOR YEARS

Children in the United States aged 12 to 15 months are routinely given rubella vaccine, and a report in the *Journal of the American Medical Association* says the vaccine-induced antibodies persist up to 16 years after immunization. Susan Y. Chu, PhD, of the Hawaii State Department of Health, Honolulu, and colleagues looked at data gathered in 1985 from 1,290 persons involved in three rubella trials initiated in 1969 in Hawaii. They found seropositivity (antibody presence) rates of 92.4 percent at the screening level generally accepted as protective against rubella, and 96.4 percent at the lowest detectable screening level. The authors note the clinical protection afforded by lower levels of rubella antibodies needs to be better defined, and suggest long-term studies "to determine whether rubella vaccine-induced immunity is lifelong or whether it continues at least throughout the critical reproductive years." But they say "evidence to date suggests that nearly all persons with detectable antibody are immune to rubella and that mass revaccination efforts are unwarranted."

JAMA June 3, 1988

INEQUALITY IN KIDNEY TRANSPLANTATION

There is age—, and sex-based inequality in kidney transplantation in the United States, says a study in June's *Archives of Internal Medicine*. The report by Carl M. Kjellstrand, MD, FACP, of the Karolinska Hospital, Stockholm, Sweden, calculates the chances of receiving a kidney transplant in the U.S. in 1983 (the last year for which complete data were available, and in the Midwest from 1979 through 1985, considering patient's age, sex and race. When race, age and sex were analyzed together, nonwhite patients aged 21 to 45 had only half the chance of receiving a transplant as white patients of the same age and sex. Women aged 46 to 60 had less than half the chance of receiving a transplant as did men of the same race and age. In all age groups, non-whites, regardless of sex, receive fewer kidney transplants than whites and, with one exception, women received fewer than men, the author says. "We believe these imbalances only partially

have a morally neutral biological, medical, social and cultural explanation and that there should be a fairer distribution of kidney transplants," he writes.

ALCOHOL AND MARIJUANA USE AMONG TRAUMA VICTIMS

Although alcohol abuse among trauma victims is well-documented, little is known about marijuana use by trauma victims. A study in June's *Archives of Surgery* suggests a significant number of trauma patients—perhaps more than one-third—may use marijuana. The report, by Carl A. Soderstrom, MD, of the Maryland Institute for Emergency Medical Services Systems, Baltimore, and colleagues used a radioimmunoassay technique to study marijuana use prior to injury in about 1,000 patients injured either as a result of motor vehicle or non-vehicular trauma. Marijuana was detected in 34.7 percent of those studied. Patients' blood alcohol levels also were checked; 33.5 percent were positive. The authors say use of one of the drugs was associated with use of the other. There was no significant difference in marijuana use between victims of vehicular and nonvehicular trauma, but alcohol was used more often by victims of motor vehicle accidents.

EYE INJURIES

The home appears to be more hazardous than the workplace when it comes to eye injuries, suggests an Israeli study in the June *Archives of Ophthalmology*. The report by Ron Koval, MD, of the Golda Medical Center, Petah-Tiqva, and Tel Aviv University, and colleagues involves a study of 2,276 patients hospitalized for eye injuries in Israel from 1981 through 1983 (excluding military injuries). More ocular injuries occurred at home (32 percent) than at work (28 percent), with domestic injuries causing blindness in almost 5 percent of the cases. Infants and retired persons were the age groups most frequently exposed to domestic injuries, with children at play the most vulnerable (nearly half of the patients were children), the report says. "Despite advances in diagnostic and therapeutic methods, ocular trauma remains a significant cause of visual loss," say the authors, who urge more emphasis on efforts to prevent such injuries.

AMA SURVEY: PHYSICIANS FAVOR WITHDRAWING LIFE SUPPORT FROM TERMINAL PATIENTS

Seventy-eight percent of U.S. physicians favor withdrawing life support systems from hopelessly ill or irreversibly comatose patients if they or their families request it, according to an American Medical Association survey to be published in the June 3 issue of *American*

Medical News.

Of the 1,000 physicians surveyed, only 15 percent opposed withdrawing life support systems, including food and water. Seven percent were unsure. This nearly mirrors the results of a 1986 AMA public opinion survey showing 73 percent of the public favored withdrawal of life support and 15 percent opposed it.

"From the day they enter medical school, physicians are taught to cherish and preserve life," said James H. Sammons, MD, AMA executive vice president. "However, there comes the time with the terminally ill or irreversibly comatose patient that the physician must step back and, at the patient's or the family's request, allow the patient to die with dignity. While physicians should never directly cause death, they must always act in the best interest of their patients and that sometimes includes allowing them to die."

Sixty-seven percent of the physicians surveyed said they had been directly involved in treating a patient where the issue of the refusal or withdrawal of life-sustaining treatment arose. Thirty-two percent said they had not.

In contrast to the number of those physicians who had been involved in such a situation, 54 percent of those surveyed were uncertain of the legal risks and responsibilities surrounding decisions to withdraw life-sustaining treatment. Forty-three percent were certain.

Although they may have been uncertain of the legal ramifications, 90 percent of those surveyed believed that physicians should initiate discussions with patients or their families on the use or withdrawal of life-sustaining treatment. Only seven percent said no.

Living wills specify patients' wishes regarding life support treatment if they become comatose. Sixty-four percent of the surveyed physicians believe that "living wills" should be available in their offices for patients' use. Twenty-five percent said no and 11 percent were unsure.

In a separate 1988 survey of 1,500 members of the general public, 56 percent of the public said they had told their families what their wishes would be concerning the use of life-sustaining treatment if they ever enter a coma from which doctors do not believe they can recover. Forty-three percent said they had not discussed the issue. However, only 15 percent of those surveyed said they had filled out a "living will"; 84 percent had not.

Of those member of the public surveyed who had either discussed the issue with their families or signed a living will, 85 percent believed their stated wishes would be followed if the situation occurred. Six percent said no and 9 percent were unsure.

The physicians surveyed were selected randomly from the AMA's Masterfile of all active U.S. physicians. The sample included appropriate percentage of both AMA members and non-members and physicians of different ages and sexes. The public survey involved interviews with 1,500 adults, using a random sample of all residential telephones in the U.S. The interviews were conducted last February by Tarrance/SRI of Houston.

INSTRUCCIONES PARA LOS AUTORES*

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

Se urge a los autores se esfuercen en perseguir claridad, brevedad, e ir a lo pertinente en sus manuscritos no importa el tema o formato del manuscrito.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y la del impresor, se requiere de los autores que sigan las siguientes instrucciones:

Manuscrito

El manuscrito completo, incluyendo las leyendas y referencias deberán estar escritos en maquina a doble espacio, por un solo lado de cada página, en TRIPLICADO y con amplio margen. En página separada deberá incluirse lo siguiente: título, nombre del autor(es) y su grado (ej: MD, FACP), ciudad donde se hizo el trabajo, el hospital o institución académica, patrocinadores del estudio, y si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse con un encabezamiento en letras mayúsculas.

Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: Introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias.

Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: Introducción, Materiales y Métodos si es aplicable, Observaciones del Caso, Discusión, Resumen (en español e inglés), Reconocimientos y Referencias.

Nomenclatura

Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea. Se usará con preferencia el sistema métrico de pesos y medidas.

Tablas

Las tablas deben aparecer en hojas separadas. Estas deben incluir el título, y el número de la tabla debe estar en romano. Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales en la tabla. Se usará en las tablas el mismo idioma en el cual está escrito el artículo. Deben limitarse las tablas a solo aquellas que contribuyan al mejor entendimiento del manuscrito.

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Las fotografías y microfotografías se someterán como copias en papel de lustre, sin montar o en transparencias. En el reverso de la figura debe aparecer el número de la figura (arábigo) y el autor. Debe indicarse la parte superior de la ilustración.

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Un abstracto no mayor de 150 palabras debe acompañar los manuscritos. Debe incluir los puntos principales que ilustren la substancia del artículo y la exposición del problema, métodos, resultados y conclusiones.

Referencias

Las referencias deben ser numeradas sucesivamente de acuerdo a su aparición en el texto. Los números deben aparecer en paréntesis al nivel de la línea u oración. Al final de cada artículo las referencias deben aparecer en el orden numérico en que se citan en el texto. Deben utilizarse solamente las abreviaturas para títulos de revistas científicas según indicadas en el "Cumulative Index Medicus" que publica la Asociación Médica Americana. Las referencias deben seguir el patrón que se describe a continuación.

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Cartas al Editor

Se publicarán a discreción de la Junta Editora. Deben estar escritas en maquina a doble espacio, no deben ser mayores de 500 palabras, ni incluir más de cinco referencias.

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The Bulletin will accept for publication contributions relating to the various areas of medicine, surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

All authors are urged to seek clarity, brevity, and pertinence in the manuscripts regardless of subject or format.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

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The entire manuscript, including legends and references should be typewritten double spaced in TRIPLICATE with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgement of financial sponsors, and if the paper has been presented at a meeting the place and date should be given.

The manuscripts should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by headings in capital letters.

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Nomenclature

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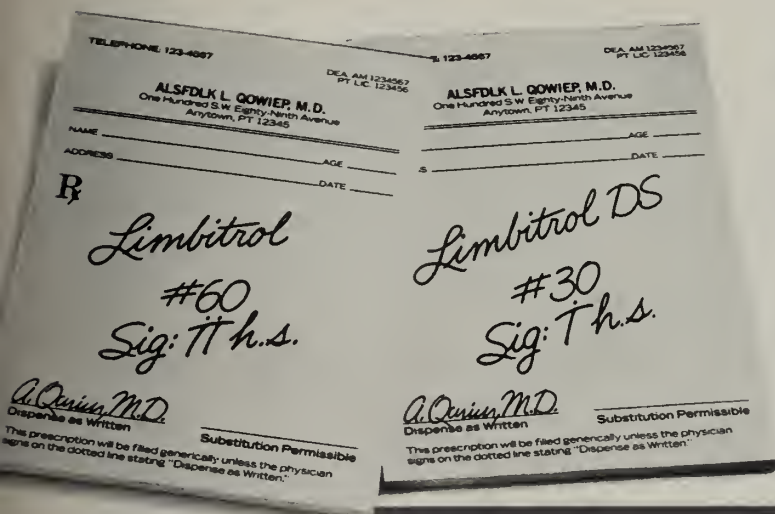
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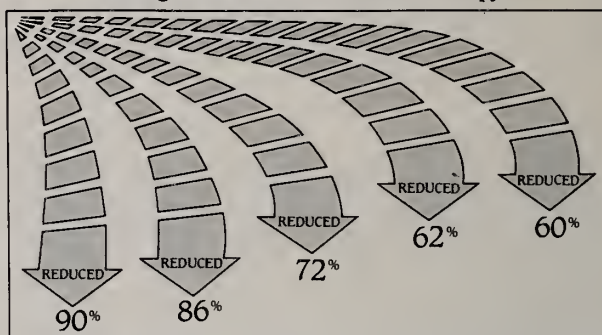
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"POSTMASTER" Send address changes to Boletín Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, Santurce, P.R. 00908.

Second Class postage paid at San Juan, P.R.

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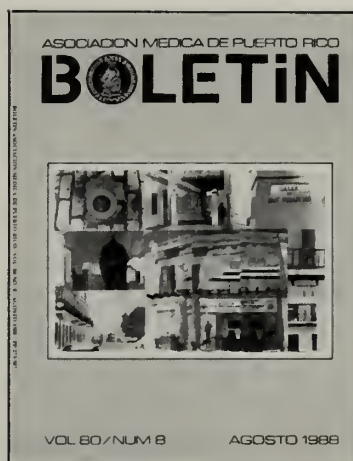
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NUESTRA PORTADA

Calle de San Sebastián. Serigrafía del artista puertorriqueño Carlos Irizarry. El autor nació en Santa Isabel, Puerto Rico hace 50 años. Su vivencia como grabador, muy influenciada por su vida en San Juan, se manifiesta en este homenaje a la ciudad de San Juan titulado Calle de San Sebastián.

La obra consta de doce colores cortados y tirados a marea por el propio artista en una tirada de 150 ejemplares. Emanan del óleo de su propia inspiración con tonalidades a tono con la labor serigráfica. Son de particular relevancia los detalles de las flores y la exhibición a estilo de tabloide de expresión pública del ya desaparecido "Hijos de Borinquen".

La obra ha sido sometida y aceptada a la bienal de San Juan que comienza el 30 de septiembre del presente año. El ejemplar utilizado para nuestra portada pertenece al Dr. Filiberto Colón-Rodríguez a quien la Junta Editora agradece su colaboración.

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ESTUDIOS CLINICOS

Liver Biopsy Findings in the Acquired Immunodeficiency Syndrome

Emilio R. González, MD
Carmen González Keelan, MD
Esther A. Torres, MD, FACP
José N. Moreno, MD

Summary: To describe the spectrum of liver disease in the Acquired Immunodeficiency Syndrome (AIDS), liver biopsy was carried out in eight patients with established AIDS. Patients were suspected of having hepatic involvement when either fever, hepatomegaly, or altered liver enzymes were present. Hepatitis profile was done in all but one patient. Liver biopsies were stained with H&E, reticulum stain, PAS, FITE stain for acid-fast bacilli, Silver stain, examined with electron microscopy for viral and bacterial particles, and all specimens were cultured for AFB and fungi. Five out of eight patients (62.5%) had a history of intravenous drug abuse, three out of eight were homosexuals (37.5%). Median age was 37 years (30-43) and mean duration of illness was eight months (2-15 months). Seven out of seven patients (100%) had a positive serology for HBV, six out of seven patients (85.7%) had a positive serology for HAV. All patients were ingesting at least one potential hepatotoxin such as ethanol or sulpha derivatives. Pathologic findings included steatosis in two out of eight (25%), granuloma in one out of eight (12.5%), chronic active hepatitis in three out of eight (37.5%). The granuloma was composed of *Schistosoma mansoni* eggs, not previously described to cause granuloma in AIDS. Bacteriologic studies were negative in all patients. We conclude that AIDS patients have a high incidence of hepatic abnormalities. No findings specific or pathognomonic for AIDS were identified in the liver.

The Acquired Immunodeficiency Syndrome (AIDS) which was defined as a disease in the 1980's, is now widely spread throughout the world, involving primarily homosexual men and intravenous narcotic users. The gastrointestinal tract is a major target organ in AIDS.¹ Both diarrhea and weight loss are common manifestations. The involvement of the liver in AIDS is only now being appreciated. Hepatomegaly is found in about two thirds of patients and there is no characteristic histologic picture. Levobics et al. found macrovesicular steatosis as

the single most common histologic finding in their series.² In contrast Orenstein et al. reported hepatic granulomas as the most common finding.³ Current data suggests that involvement of the liver with mycobacterial and fungal disease may be a frequent feature in AIDS, and therefore liver biopsy may be helpful in AIDS patients with unexplained fever, hepatomegaly and abnormal liver functions tests.⁴

The purpose of this study was to describe the spectrum of liver disease in AIDS, correlate clinical and pathologic findings, define the role of liver biopsy in the evaluation of AIDS patients, and to try to find any pathologic feature characteristic of AIDS patients.

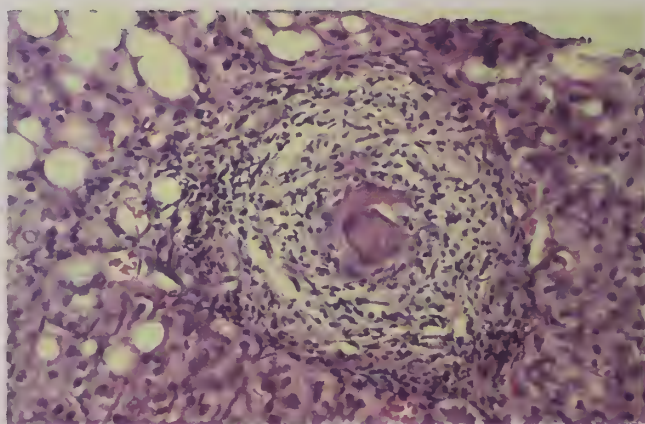


Figura 1. *Schistosoma* granuloma

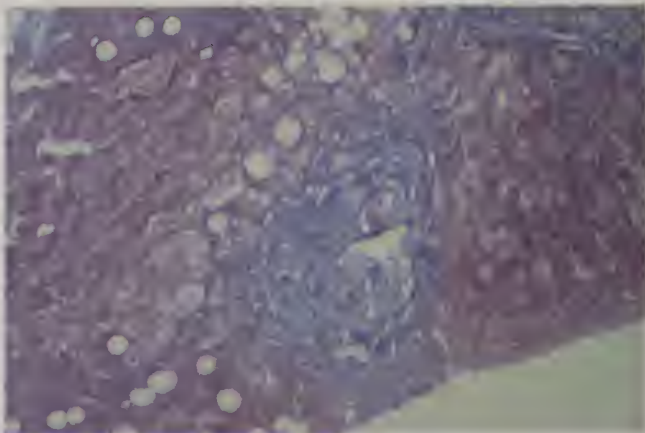


Figure 2. Trichromic stain showing chronic hepatitis with fibrosis

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Partially supported by Biomedical Research Support Grant, Reprints requests to Department of Medicine Gastroenterology Section, U.P.R. School of Medicine

Materials and Methods

All patients with AIDS admitted to the San Juan City Hospital and University Hospital who underwent a liver biopsy from October 1, 1986 to April 30, 1987 were included in this study.

All patients fulfilled the Center for Disease Control criteria for AIDS, including anergy panel, T lymphocyte subset ratio and depressed mitogen responses.⁴ Patients with AIDS Related Complex were excluded. Indications for liver biopsy were the following: unexplained fever, hepatomegaly and/or altered liver enzymes.

Clinical information was obtained from the medical records. Information regarding opportunistic infections, malignancies, hepatitis B virus marker studies (HBsAg, HBsAb, HBcAb) and complete history and physical examination were obtained by one of the authors. The use of hepatotoxic agents and/or alcohol within 3 weeks preceeding liver biopsy was recorded, as well as information regarding fever, hepatomegaly and liver function tests.

Fever was defined as oral temperature of at least 100.5°F. Liver size was measured by physical exam. Biochemical liver tests included ALT, AST, alkaline phosphatase, total bilirubin level, and were considered abnormal if results were 1.5 times the upper limit of the normal range.

All liver biopsy specimens were stained with:

1. Hematoxylin and eosin
2. Reticulum stain
3. Periodic acid-Schiff
4. FITE stain for acid fast mycobacteria
5. Silver stain for fungi

They were examined under electron microscopy for viral and bacterial particles and specimens were cultured for AFB and fungus.

Demographic features of our patients are shown in Table 1. Eight patients were studied. Age ranged from 30 to 40 years (mean 37 years). All patients were male. Three patients (37.5%) were homosexual and five patients (62.5%) were intravenous drug abusers. All patients had opportunistic infections. The mean duration of illness at the time of liver biopsy was eight months (range: 2-15 months). There was no history of previous blood transfusions in any of our patients.

Results

All patients tested for hepatitis B markers were positive (7/7), six out of seven patients (85.7%) had positive serology for Hepatitis A virus. All patients were ingesting at least one potential hepatotoxin (ethanol or sulfa derivatives)

Six out of eight AIDS patients had hepatic abnormalities on liver biopsy: steatosis was present in two (25%), granuloma in one (12.5%) and chronic active hepatitis in three (37.5%). Electron microscopy did not reveal viral or bacterial particles. Bacteriologic studies were negative for AFB and fungi in this study group.

Table 1

Demographic Features					
Patient	Age	Sex	Risk Factor	Opportunistic Infection	*Duration of Illness
1	40	M	H.S.	PCP	9
2	38	M	IVD	H. zoster PCP	6
3	36	M	H.S.	Disseminated cryptococcosis	7
4	43	M	IVD	PCP	11
5	42	M	H.S.	PCP Oral candidiasis	15
6	31	M	IVD	PCP	2
7	39	M	IVD	Suspected toxoplasmosis PCP	10
8	30	M	IVD	PCP	4

*Refers to duration of illness at the time of liver biopsy (in months)

H.S. - homosexual

I.V.D. - intravenous drug use

P.C.P. - *Pneumocystis carinii* pneumonia

Median age: 37 years

Risk factors: 37% H.S., 63% I.V.D.

Duration: mean 8 mo. (2-15 months)

Table 2

Clinical Indications for Liver Biopsy and Pathologic Findings							
Fever	Hepatomegaly	ALT	AST	AP	T.B.	ALB.	Pathology
1. No	No	37	20	378	2.1	2.2	Mild Steatosis
2. No	No	53	56	277	0.2	2.7	Schistosoma granuloma
3. No	No	61	62	206	0.3	3.1	H&E normal
4. No	No	80	65	269	0.9	2.6	CAH
5. No	No	19	47	77	0.2	2.5	Mild steatosis Mild cholestasis
*(475)							
6. No	No	77	61	122	0.2	3.1	Normal
7. No	No	31	50	211	0.1	2.6	CAH
8. No	No	18	115	350	4.6	1.9	CAH

ALT - Alanine aminotransferase

AST - Aspartate aminotransferase

AP - Alkaline phosphatase

T.B. - Total bilirubin

*GGT - Gamma glutamyl transpeptidase

ALB - Albumin

CAH - Chronic active hepatitis

Discussion

The spectrum of liver disease we encountered in this series of patients with AIDS was broad.

Liver involvement could be attributed to nonspecific changes related to chronic illness, complications, either infectious or iatrogenic or concomitant liver disease secondary to alcohol abuse or viral exposure.^{1, 7}

Seventy six percent of AIDS patients showed hepatic abnormalities such as steatosis, granuloma and chronic active hepatitis. In spite of our high prevalence of IV drug abuse in our study population, we found only one patient with hepatic granuloma. This was shown to be secondary to *Schistosoma mansoni*, a previously unrecognized

cause of granuloma in AIDS patients. The low incidence of hepatic granulomas in our series may be explained by two facts. First, it has been described that the incidence of hepatic granuloma is high in patients with disseminated or pulmonary mycobacterial infections.³ Second, our patients had a mean duration of disease of eight months at the time of biopsy, making the formation of granulomas unlikely, as suggested recently by Orenstein et al.⁵

We also found an unexpectedly high incidence of chronic active hepatitis (38%), as compared to 3-5% previously reported.⁶ The low incidence of chronic active hepatitis in AIDS patients has been postulated to be due to the altered T lymphocyte function influencing the course of liver disease in these patients.

Although were found a high prevalence of liver abnormalities in patients with AIDS, no finding specific or pathognomonic for AIDS was identified in the liver, and no clinicopathologic correlation was found. Liver biopsy in this population should be individualized according to the clinical picture. A larger group of patients should be studied to evaluate further the significance of our data.

Resumen: Ocho pacientes con SIDA fueron sometidos a biopsia de hígado para determinar el espectro de enfermedad de hígado en esta condición. Las indicaciones para biopsia fueron fiebre, hepatomegalia o alteración en las enzimas hepáticas. En siete pacientes se realizó prueba de perfil de hepatitis. Las biopsias se tiñeron con H&E, reticulina, PAS, tinte FITE para bacilos ácido-resistentes y plata, se examinaron por microscopía electrónica y todas se cultivaron para bacilos ácido-resistentes y hongos. Cinco de 8 pacientes (62.5%) tenían historial de abuso de drogas intravenosas, 3 (37.5%) eran homosexuales. La edad media era de 37 años (30-43), y la duración de enfermedad era de 8 meses (2-15). Siete (100%) tenían algún marcador de hepatitis B, 6 de 7 (85.7%) tenían anticuerpos de hepatitis A. Todos los pacientes estaban recibiendo por lo menos un agente hepatotóxico. Los hallazgos histológicos incluyeron hígado graso (2/8), granulomas de schistosomiasis (1/8), hepatitis crónica activa (3/8). Los estudios de bacteriología fueron negativos en todos. Concluimos que los pacientes con SIDA tenían una incidencia alta de anomalías hepáticas, pero no se identificaron cambios hepáticos específicos o patognomónicos.

SE ALQUILA

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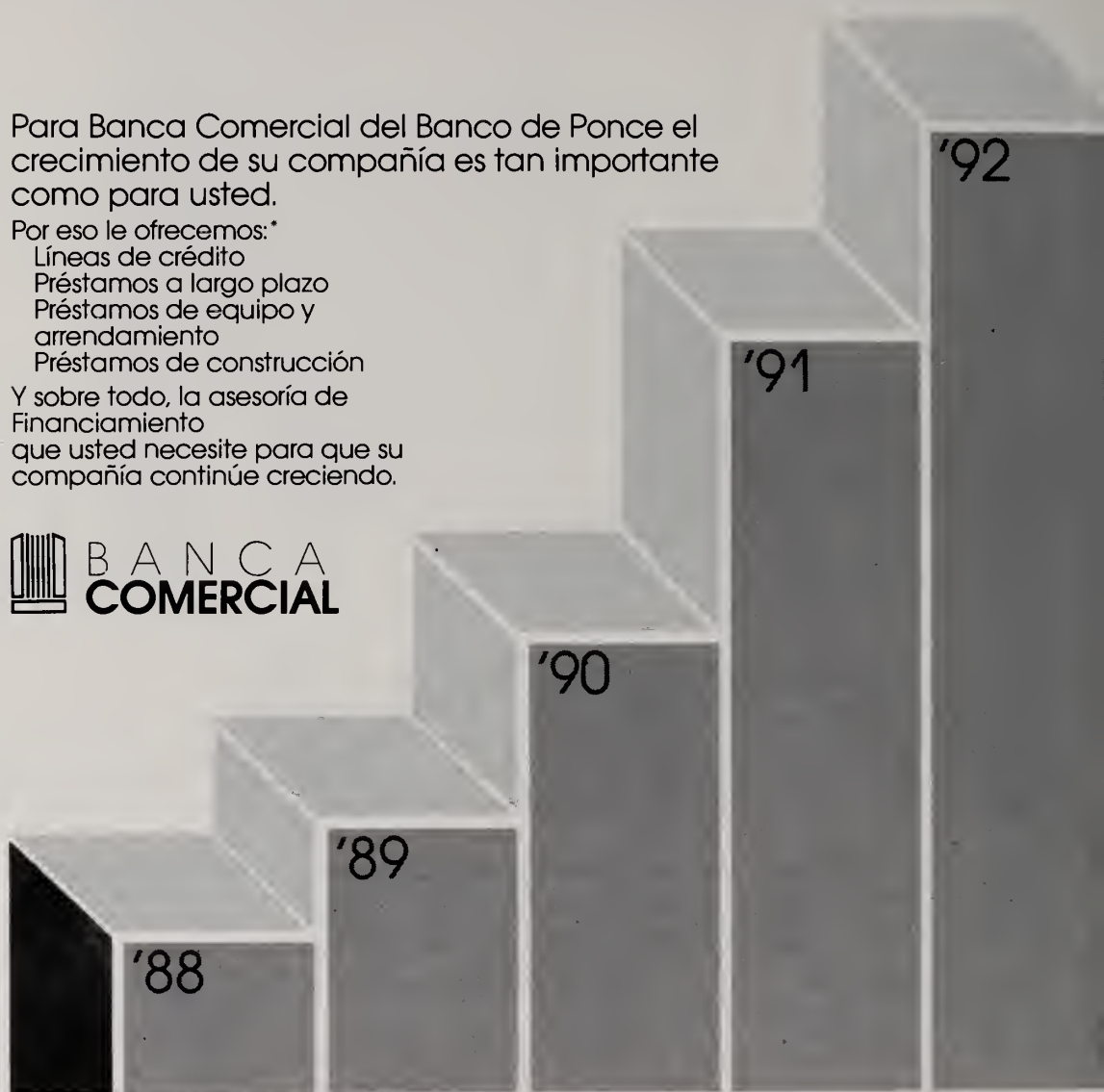
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**In vitro* activity does not necessarily imply a correlation with *in vivo* results.

[†]Due to susceptible strains of indicated pathogens. See indicated organisms in Brief Summary.

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BRIEF SUMMARY CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION INDICATIONS AND USAGE

Cipro[®] is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Lower Respiratory Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*.

Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (penicillinase and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, and *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri*, and *Shigella sonnei* when antibacterial therapy is indicated.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with Cipro[®] may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN SHOULD NOT BE USED IN CHILDREN OR PREGNANT WOMEN The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and norfloxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (SEE ANIMAL PHARMACOLGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

General:

As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and very rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals. Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded. Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

Drug Interactions:

Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin, resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

Probenecid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients:

Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum concomitantly or within two hours after dosing. Ciprofloxacin may cause dizziness or lightheadedness; therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

- Salmonella/Microsome Test (Negative)
- E. coli* DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V₇₉ Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- Saccharomyces cerevisiae* Point Mutation Assay (Negative)
- Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the following three *in vivo* test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Micronucleus Test (Mice)
- Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in animals have not yet been completed.

Pregnancy - Pregnancy Category C:

Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in

CONVENIENT B.I.D. DOSAGE

Recommended dosage schedule

Infection Site*	Severity of Infection	Dosage
Respiratory Tract*	Mild/Moderate	500 mg B.I.D.
Bone and Joint*		
Skin/Skin Structure*	Severe/Complicated	750 mg B.I.D.
Urinary Tract*	Mild/Moderate	250 mg B.I.D.
	Severe/Complicated	500 mg B.I.D.
Infectious Diarrhea*	Mild/Moderate/Severe	500 mg B.I.D.

pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers:

It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Ciprofloxacin should not be used in children because it causes arthropathy in immature animals (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%).

The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%), vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and rash (1.1%). Additional events that occurred in less than 1% of ciprofloxacin courses are listed below. Those typical quinolones are italicized.

GASTROINTESTINAL: (See above), painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM: (See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.

SKIN/HYPERSENSITIVITY: (See above), pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

SPECIAL SENSES: blurred vision, disturbed vision, (change in color perception, overbrightness of light), decreased visual acuity, diplopia, eye pain, tinnitus, bad taste.

MUSCULOSKELETAL: joint or back pain, joint stiffness, achiness, neck or chest pain, flare-up of gout, RHEUMATISM: interstitial nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR: palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY: epistaxis, laryngeal or pulmonary edema, hiccup, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to dose relationship.

Hepatic - Elevations of: ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Hematologic - eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal - Elevations of: Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: Elevation of serum gamma-glutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. In the event of serious toxic reactions from overdosage, hemodialysis or peritoneal dialysis may aid in the removal of ciprofloxacin from the body, particularly if renal function is compromised.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro[®] (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and Unit-Dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE INFORMATION).

* Due to susceptible strains of indicated pathogens. See indicated organisms in Brief Summary.

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ESTUDIOS EXPERIMENTALES

Efectos de la Extirpación Estereotaxica del Nucleo Amigdalino Basolateral sobre la Ultraestructura del Nucleo Hipotalámico Ventromedial

Alfonso López-Muñiz, MD
Jacinto de Miguel, MD
Antonio Pérez-Casas, MD

Resumen: Hemos empleado 40 ratas macho, cepa Wistar, de 2 meses de edad. Los animales se dividieron en 20 ratas controles (10 ratas intactas y 10 ratas sometidas a operación simulada), y 20 animales experimentales (10 sacrificados al mes y 10 sacrificados a los dos meses de la operación quirúrgica).

El método experimental fue la extirpación estereotaxica del nucleo amigdalino basolateral de la amígdala cerebral. Hemos estudiado la ultraestructura del nucleo ventromedial del hipotálamo. Hemos observado un incremento de la actividad de las neuronas del nucleo hipotalámico ventromedial en los animales experimentales (aumento del retículo endoplasmático rugoso, del aparato de Golgi, de los cuerpos densos, y de las mitocondrias con matriz densa), y en las sinapsis (un incremento de las vesículas y de los gránulos densos).

Nuestros resultados demuestran que el nucleo amigdalino basolateral ejerce un efecto inhibitor de la actividad neuronal del nucleo hipotalámico ventromedial.

Numerosos trabajos justifican la influencia de la amígdala en la secreción endocrina, y especialmente en la esfera gonadotropa.^{1, 2, 3, 4} En los mismos se demuestra que la destrucción de la amígdala lleva a una disminución de los parametros de actividad gonadal,¹⁻³ mientras que su estimulación produce un aumento de los mismos.⁴

Posteriores trabajos encontraron que la función de la amígdala era distinta de unos a otros de sus nucleos debido a que el complejo amigdalino esta formado por

varios nucleos y sus vías de conexión con el hipotálamo son distintas de unos a otros de ellos.^{5, 6, 7}

En este sentido algunos autores consideran que solo la amígdala corticomedial facilita la producción de gonadotropinas, mientras que la amígdala basolateral inhibe la misma.^{8, 9, 10}

Igualmente se piensa que las porciones amigdalinas corticomedial y basolateral tienen funciones opuestas en el control de la elaboración de hormona de crecimiento.¹¹

Por otro lado algunos autores proponen que el control hipotalámico de las actividades gonadotrópica y somatotrópica recae fundamentalmente en los nucleos arqueados e hipotalámico ventromedial.^{12, 13, 14, 15} Sin embargo no sabe con certeza como se media este control, ya que el hipotálamo implicado en dicha función recibe conexiones de ambas porciones amigdalinas y por ambos sistemas de conexión (vía amígdalo-ventrofugal y vía amígdalo-dorsofugal).^{5, 6, 7}

En consecuencia, no es bien conocida la influencia de la amígdala cerebral en la secreción endocrina, así como el nivel de integración de los diferentes impulsos que desde las distintas áreas nucleares de la amígdala alcanzan el hipotálamo.

Por este motivo nos hemos propuesto estudiar, el nucleo hipotalámico ventromedial en animales a los que se les había destruido el nucleo amigdalino basolateral, que es el de mayor importancia funcional en la porción amigdalina homónima.

Material y Métodos

Hemos empleado 40 ratas macho, cepa Wistar, de edades comprendidas entre 8 y 10 semanas, y pesos entre 200 y 250 gm.

Todos los animales, controles y experimentales, fueron sometidos a las mismas condiciones ambientales (luminosidad, temperatura, humedad...) y alimentados con agua potable "ad libitum", y pienso específico para ratas y ratones.

Los animales fueron clasificados en tres grupos:

Departamento de Morfología y Biología Celular, Facultad de Medicina, Universidad de Oviedo, España.

Solicitar sobretiros a: Prof. Alfonso López-Muñiz, Departamento de Morfología y Biología Celular (Anatomía) — Facultad de Medicina — c/Julián Clavería s/n. 33006- OVIEDO

Este estudio pertenece a un proyecto de investigación subvencionado por la CAICYT, el Ministerio de Educación y Ciencia Nacional y la Universidad de Oviedo.

1. Animales controles, formado por los animales intactos (10) y los animales sometidos a operación simulada (10).

2. Animales sometidos a amigdalectomía basolateral bilateral y sacrificados al mes de su intervención: Animal Experimental Grupo A (10 ratas).

3. Animales sometidos a amigdalectomía basolateral bilateral y sacrificados a los dos meses de ser intervenidos: Animal Experimental Grupo B (10 ratas).

Método Experimental

Los animales son anestesiados con pentobarbital sódico (Nembutal) 40 mg/kg de peso. Trás su fijación procedemos a la intervención por estereotaxia, para la cual hemos empleado un aparato de estereotaxia, marca LPC, y utilizando para la localización de las estructuras el atlas topográfico del cerebro de rata de L.S. Pellegrino: A.S. Pellegrino; A.J. Cushman (Ed. Plenum Press/New York 1981).

Una vez preparado el animal en el aparato de estereotaxia, localizamos el punto Bregma desplazando la aguja 1mm hacia detrás; 5.2 mm. lateralmente y 7.5 mm en profundidad.

Hemos empleado una descarga de 2 miliamperios durante 20 segundos.

La intervención se realiza bilateralmente. Tal como indicaremos, al sacrificar a los animales comprobamos la intervención sobre el complejo nuclear amigdalino, procediéndose al estudio de aquellos en los que la operación fuera correcta y despreciándose las restantes ratas.

En los animales controles de operación simulada se realiza el mismo proceso pero no se aplica la descarga eléctrica.

Técnica de la Microscopia Electrónica

Tras ser anestesiados (Nembutal), todos los animales son perfundidos en el ventrículo izquierdo usando una serie estandar de soluciones intravenosas. La perfusión se realiza a una presión aproximada de 100 mm Hg.

Se emplea una solución salina previa (solución salina normal con 1 cc de heparina sádica por 100 ml.) para la vasodilatación del sistema circulatorio del animal hasta obtener un retorno limpio en la aurícula derecha. Inmediatamente se perfunde glutaraldehído al 2.5% en buffer fosfato (ph. 7.4).

Las piezas se tallan en bloques de 1 mm. y son posfiadas en una mezcla de glutaraldehído al 2.5% en buffer fosfato (pH 7.4) durante 1 hora a 4 grados. A continuación se tratan en otra solución tamponada a 4 grados durante 12 horas y finalmente con una solución de tetróxido de osmio tamponado en fosfato a pH. 7.4 durante 2 horas.

Los tejidos son deshidratados en una serie de alcoholes etílicos de graduación creciente, aclarados con óxido de propileno, y embebidos en EPON.

Se realizan cortes semifinos desde el polo anterior al posterior del cerebro para localizar la amígdala (donde se comprueba que la intervención ha sido correcta) y posteriormente el hipotálamo donde se localiza la región

nuclear a estudiar. Posteriormente se realizan cortes ultrafinos a 50 nm.

Las secciones fueron coloreadas con acetato de uranilo y citrato de plomo y examinadas con un microscopio electrónico Zeiss EM9A.

Resultados

Animales Controles

Tanto en los animales intactos como en los de operación simulada la población celular se compone de dos tipos neuronales: neuronas claras, cuyo núcleo tiene escasa cromatina y en el citoplasma destacan las membranas del retículo endoplasmático, rico en ribosomas; el aparato de Golgi poco desarrollado; las mitocondrias alargadas y estrechas; la existencia de cuerpos redondeados y osmófilos (Fig. 1); neuronas oscuras con núcleos de cromatina granular abundante (frecuentemente nucleolo); mitocondrias de pequeño tamaño; aparato de Golgi poco desarrollado; y abundan-

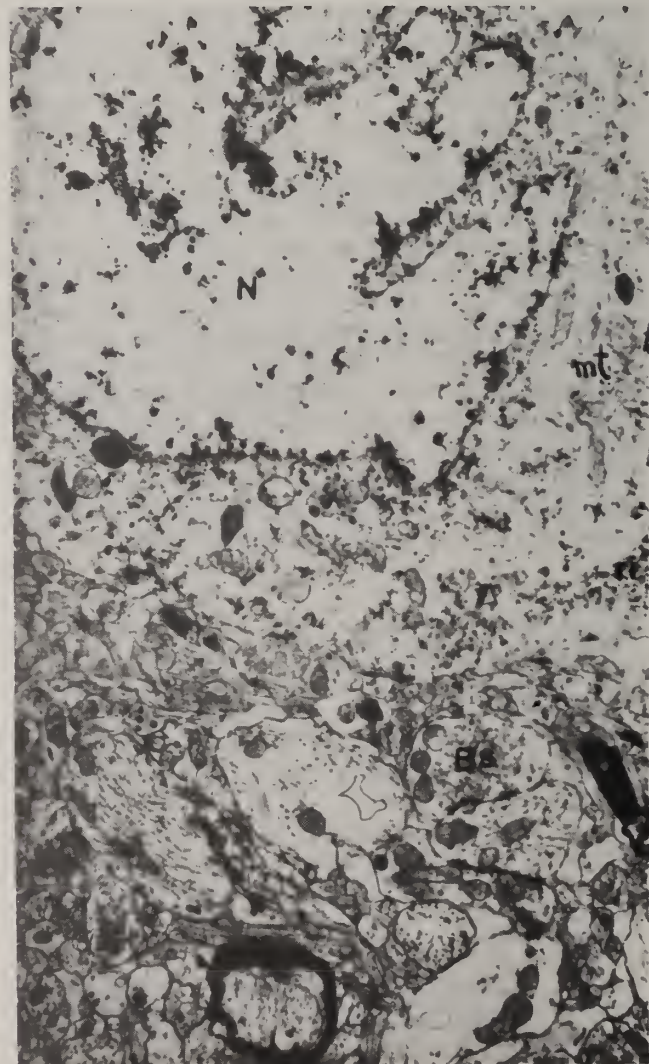


Figura 1. Animal control. 5.000X.

Detalle de una neurona clara, cuyo núcleo presenta numerosas invaginaciones y escasa cromatina; y en cuyo citoplasma hay escasas organelas (mitocondrias, ribosomas...).

tes ribosomas agrupados en la proximidad del retículo endoplasmático rugoso (Fig. 2).

Se observan numerosas sinapsis axo-somáticas y axo-dendríticas, que pueden ser en ambos casos tipo I ó II de Golgi, con contenido presináptico (numerosas vesículas unas de 600 y otras de 900 Å) (Fig. 3).

No se observó ninguna diferencia entre los animales controles intactos y los animales sometidos a operación simulada.

Animal Experimental Grupo A

En las neuronas del núcleo ventromedial (NVM) se observa un gran desarrollo del complejo de Golgi, formado por sáculos y vesículas en número muy elevado, extendiéndose por todo el citoplasma celular, y pudiendo apreciarse la existencia de gránulos de secreción (Fig. 4).

Son muy abundantes los ribosomas, que se suelen localizar en las proximidades de la carioteca o de las membranas golgianas, y el retículo endoplasmático, observándose con frecuencia la existencia de retículo endoplasmático rugoso (Fig. 5)

Las mitocondrias están escasamente alteradas, pero en ocasiones se observan alteraciones en su morfología (alargamientos...) (Fig. 4).

El hallazgo más llamativo, en este grupo experimental, ha sido la presencia en el citoplasma de numerosas polisomas, pequeños gránulos de secreción (900-1200 Å de diámetro) y cuerpos densos, tanto en las neuronas claras, como en las oscuras. (Fig. 6).

Animal Experimental Grupo B

Destaca el gran desarrollo del aparato de Golgi en cuya proximidad se aprecian cuerpos densos, mitocondrias y formaciones multivesiculares (Fig. 7).

Las mitocondrias son alargadas, estrechas, y con matriz densa. Se evidencia la relación existente entre los gránulos densos, y las cisternas/vesículas del complejo de Golgi (Fig. 7).

También existe un incremento del retículo endoplasmático rugoso que presenta acúmulos de cisternas dilatadas y aplanadas (Fig. 8).

En ocasiones se interponen entre las cisternas de retículo endoplasmático, polisomas y cuerpos densos de distinto tamaños (Fig. 9).

Los cuerpos densos, que frecuentemente se relacionan con las zonas golgianas, tienen en su interior contenido granular o estructuras paracristalinas (Fig. 9).

Todas estas alteraciones son observables en las neuronas claras y oscuras, aunque son más evidentes en las segundas por poseer estas más organelas citoplasmáticas.

En la zona de las sinapsis se observan en los animales experimentales de este grupo, un aumento en el número de estructuras densas, especialmente en las sinapsis axo-dendríticas tipo I de Golgi, con la presencia en las regiones sub-sinápticas de aparatos-cisternas-formaciones de retículo endoplasmático liso, en forma de vesículas inter-relacionadas entre sí por material denso de diámetro entre 600 y 1100 Å (Fig. 10).

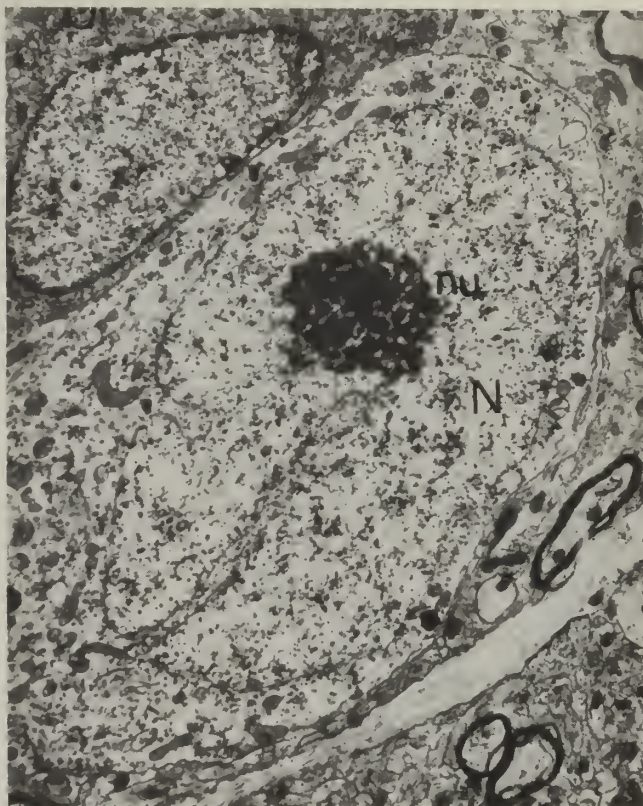


Figura 2. Animal control. 1.800X

Imagen de una neurona oscura, cuyo núcleo presenta un desarrollado nucleolo, y en su citoplasma hay numerosos organelas (mitocondrias...). Observe que en los animales controles el complejo de Golgi es de pequeñas dimensiones. En parte superior de la imagen se aprecia la existencia de un oligodendrocito.

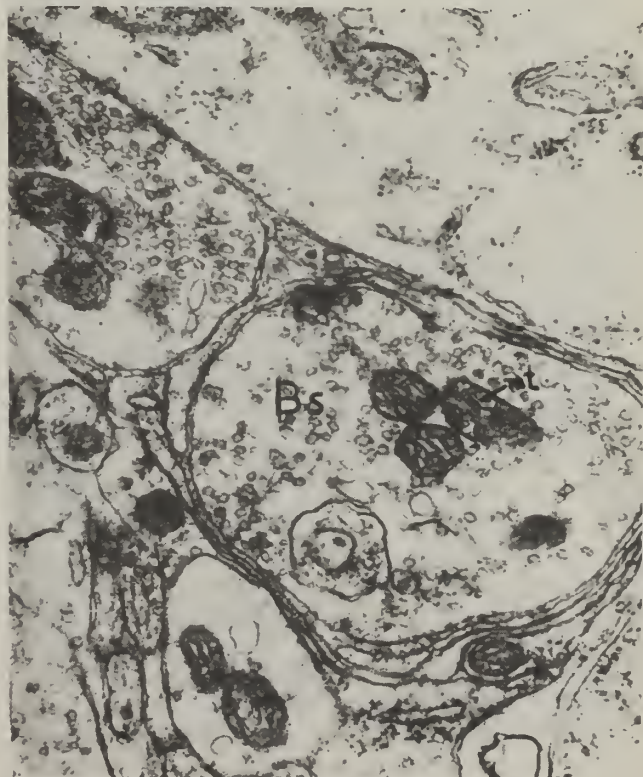


Figura 3. Animal control. 36.000X.

Se demuestran dos sinapsis tipo II de Gray, con estructuras granulares y mitocondrias.

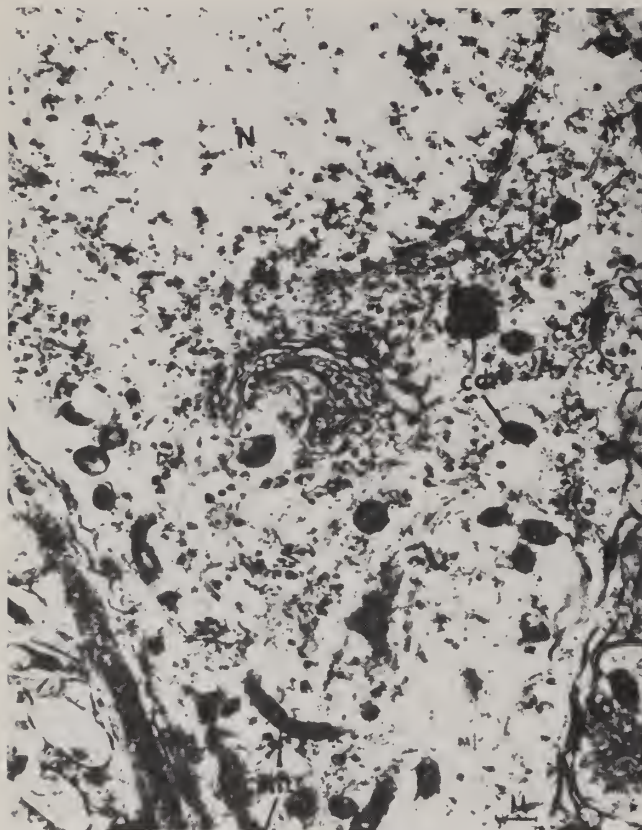


Figura 4. Animal experimental Grupo A. 2.800X.
Se observa una porción del citoplasma neuronal donde destaca la existencia de un complejo de Golgi bien desarrollado y numerosos cuerpos densos.

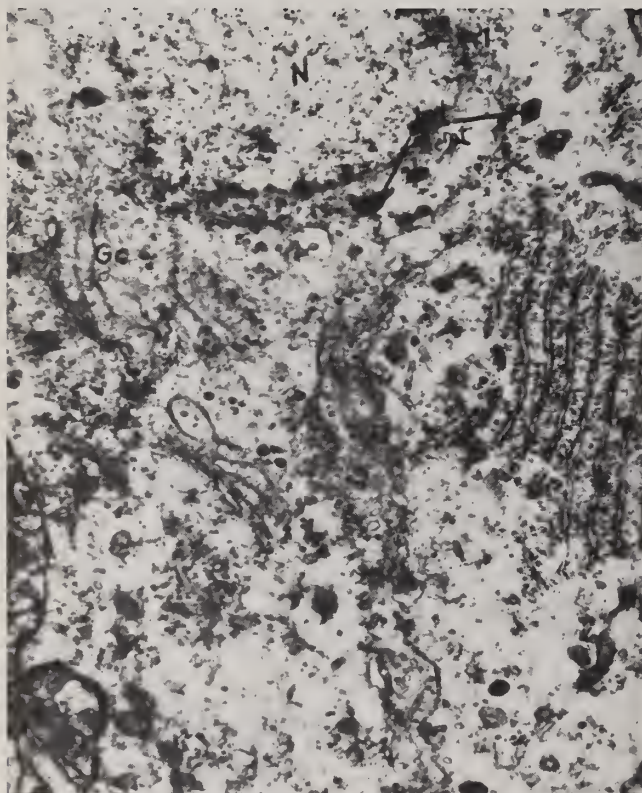


Figura 5. Animal experimental Grupo A. 3.000X.
Imagen semejante a la anterior donde se aprecia el gran desarrollo del complejo de Golgi y de las cisternas de retículo endoplasmático rugoso, así como el aumento de los cuerpos densos.



Figura 6. Animal experimental Grupo A. 3.000X.
En el citoplasma de una neurona se observa el incremento de las vesículas del aparato de Golgi y en su proximidad el aumento de los gránulos de secreción y de los cuerpos densos.

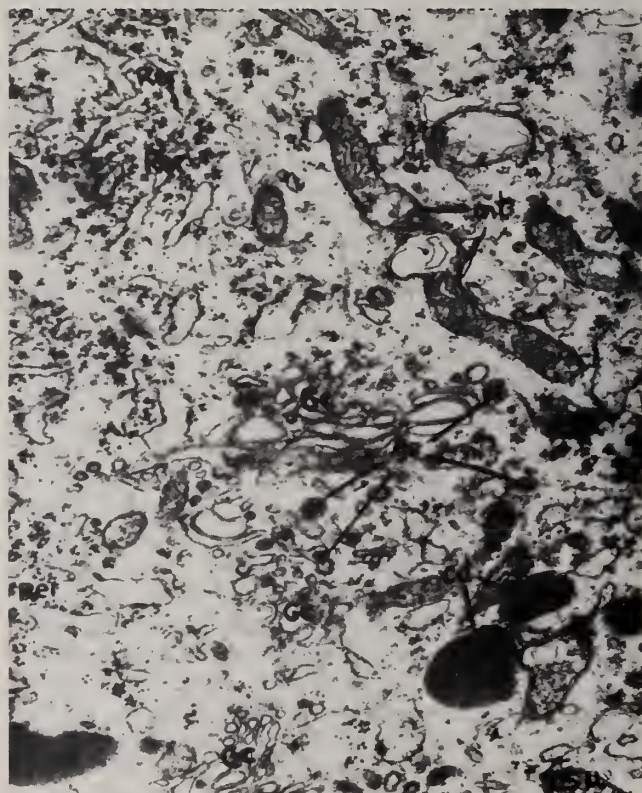


Figura 7. Animal experimental Grupo B. 70.000X.
Se observa una neurona que presenta un aumento de su actividad citoplasmática, con gran desarrollo de las estructuras golgianas, cuerpos densos y gránulos de secreción.

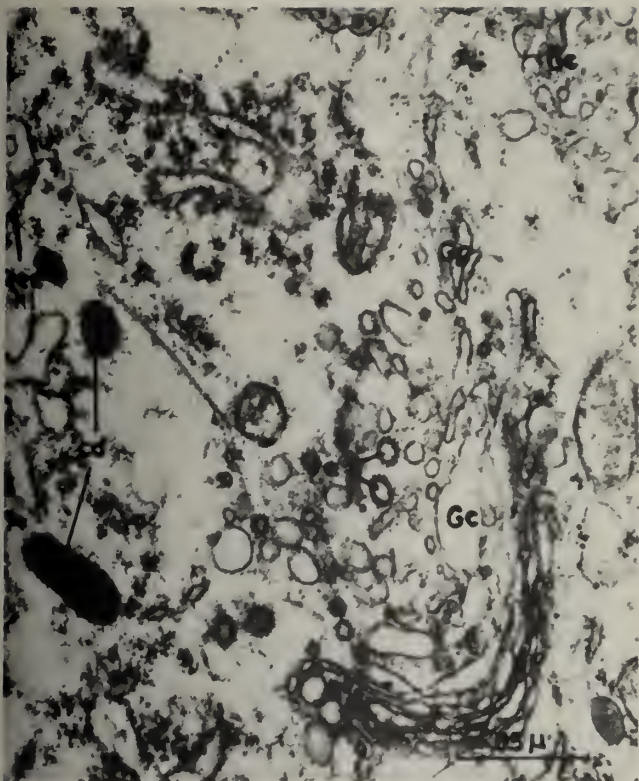


Figura 8. Animal experimental Grupo B. 70.000X.
A mayor aumento se observan los cuerpos densos con su estructura de membrana y su contenido paracristalino.

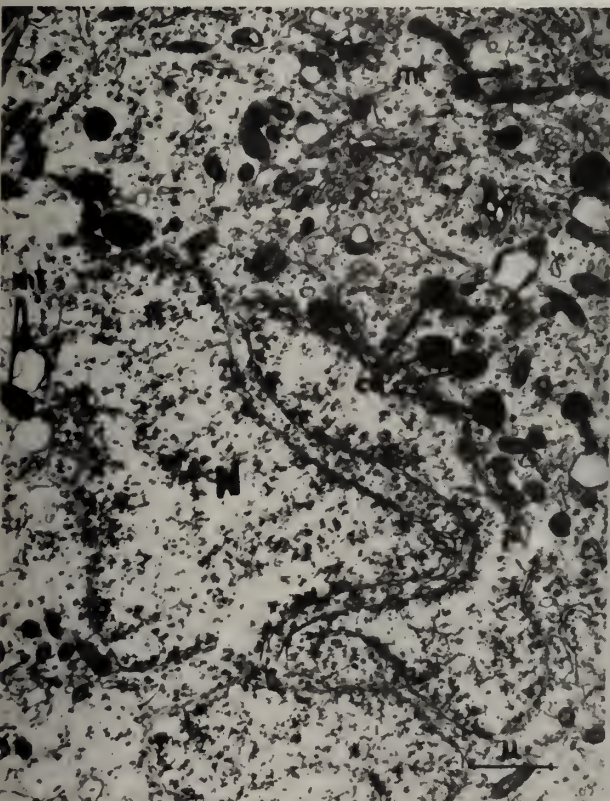


Figura 9. Animal experimental Grupo B. 7.000X.
Neurona cuyo núcleo presenta invaginaciones de la carioteca, y en su citoplasma hay un notable incremento del retículo endoplasmático rugoso y del aparato de Golgi, así como de las estructuras con él relacionadas (cuerpos densos...).

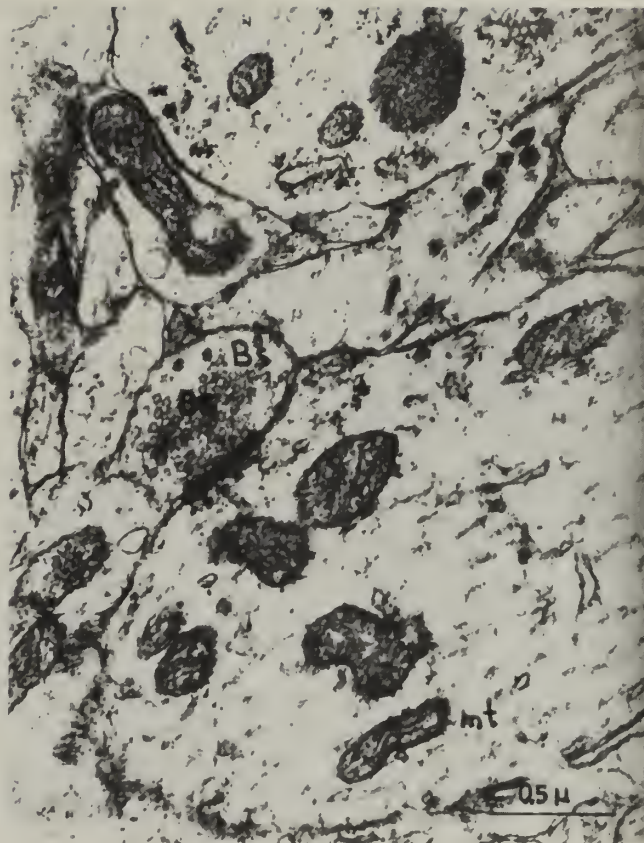


Figura 10. Animal experimental Grupo B. 36.000X.
Sinapsis axo-dendrítica tipo I; que muestra un aumento del grosor de la membrana subsináptica y de las formaciones densas próximas.

Discusión

Nuestros resultados demuestran un notable aumento en la actividad de las neuronas del NVM, que es más acusada en los animales experimentales del Grupo B que en los del Grupo A. Es decir, dicho aumento de la actividad se incrementa con el tiempo de latencia, siendo mayor a los dos meses que al mes de realizar la exeresis bilateral de los núcleos amigdalinos basales.

Ya que la destrucción del núcleo amigdalino basolateral origina un aumento de todos los parámetros citofisiológicos (aumento de las mitocondrias, incremento de las membranas endoplasmáticas y de las estructuras densas de las sinapsis...), los estímulos del grupo nuclear amigdalino basolateral ejercen un efecto inhibitor de la actividad de las neuronas del NVM.

En resumen, podemos afirmar que el núcleo ventromedial, (NVM) es un nivel de integración de los impulsos amigdalinos que controlan el hipotálamo hipofisiotropo, y por tanto la secreción endocrina, siendo el núcleo amigdalino basolateral quien inhibe o frena la actividad de las neuronas del núcleo hipotalámico ventromedial.

Ya que las neuronas del NVM ejercen el control hipotalámico de la secreción gonadotrópica y somatotrópica,^{12, 13, 14, 15} un aumento en la actividad de dichas neuronas debe relacionarse con un aumento en la producción de factores liberadores hipotalámicos de gonadotropinas.^{12, 13, 14, 15}

Por otro lado sabemos que el control amigdalino de estas secreciones es doble, ya que algunos núcleos de la amígdala inhiben mientras que otros estimulan la elaboración de dichas hormonas, sin que se supiera el papel de cada una de las porciones amigdalinas ni su nivel hipotálamico de integración.^{8, 9, 10, 11}

Nuestros resultados nos permiten afirmar que el núcleo amigdalino basolateral tiene una función inhibidora, la cual se integra a nivel hipotálamico en el NVM. Otros autores también han considerado el núcleo hipotálamico ventromedial y el núcleo arqueado como lugares de integración de impulsos preópticos con el sistema límbico,¹²⁻¹³ y posiblemente intervenga en el control inhibidor de las secreciones endocrinas gonadotrópica y somatotrópica.

Summary: Forty male rats of the Wistar strain, two months old, were used in this study. The rats were divided into twenty control rats (ten undamaged rats and ten simulated operation rats) and twenty experimental rats. Ten rats were sacrificed one month and ten rats were sacrificed two months after the surgical operation.

The experimental rats were subject to the stereotaxic ablation of the basolateral nucleus of the amygdaloid body. We studied the fine structure of the ventromedial nucleus of the hypothalamus. We observed an increase in the activity of the hypothalamic ventromedial nucleus neurons in the experimental animals (an increase of the rough endoplasmic reticulum, Golgi apparatus, dense bodies and mitochondria with dense matrix); and in the synaptic boutons (an increase of the dense granules and the vesicles).

These results allow us to conclude that the amygdalar basolateral nucleus exerts an inhibitory influence on the activity of the hypothalamic ventromedial nucleus.

Abreviaturas de Ilustraciones

Bs.-botón sináptico	N.-núcleo.
cd.-cuerpo denso.	nu.-nucleolo.
Gc.-complejo de Golgi.	ol.-oligodendroglia.
GC.-astroglia.	r.e.r.-retículo endoplasmático rugoso.
gs.-gránulo de secreción.	ri.-ribosoma.
mt.-mitochondria.	ve.-vesícula espinosa.

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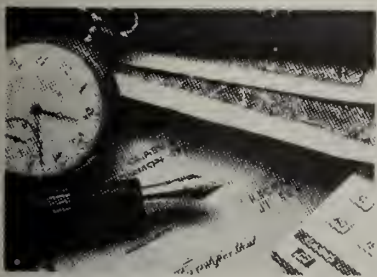
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Case Presentation

Tricuspid Valve Vegetation Simulating an Intracardiac Tumor

Roberto Pérez, MD
Charles Johnson, MD, FACC

Abstract: Two-dimensional echocardiography is an important tool in the diagnosis and differentiation of intracardiac masses, but it should always be incorporated within the clinical setting for a correct diagnosis. We report a patient with a large tricuspid valve vegetation that resembled a right heart tumor, especially a myxoma, on two-dimensional echocardiography.

When a mass effect is seen by two-dimensional echocardiography in the tricuspid valve (TV) area, several possibilities arise: a TV vegetation, a tumor (e.g. myxoma, fibroelastoma or a thrombus). The clinical picture is the most important element in the differentiation of these entities, since echocardiographic findings may not be specific enough to make a distinction between them.

We report a case of TV endocarditis in which the echocardiographic findings suggested a tumor, most likely a myxoma. Our purpose is to emphasize the limitations of echocardiography in the differentiation of intracardiac masses.

Case Report

This is the case of a 31 years old white male patient with a history of intravenous drug abuse (cocaine), who was admitted to a community hospital with a three-weeks history of low-grade fever, general malaise, and shortness of breath. A diagnosis of acute bacterial endocarditis was made and the patient was treated with nafcillin and gentamicin. At the time of blood sampling for culture he had been using oral antibiotics erratically, and all cultures were negative. A two-dimensional echocardiogram revealed a 2 cm highly mobile mass in the TV area that could be seen intermittently in the right atrium as well as in the right ventricle. No Doppler examination was done.

In the hospital he had an episode of chest pain, hemoptysis, and pulmonary embolism was confirmed

with ventilation and perfusion lung scans. At this time he was transferred to the University Hospital for further management.

At physical examination he had occasional low grade fever and a grade 1/6 systolic murmur at the fourth left intercostal space that varied in intensity with changes in posture and respiration. The jugular venous pulsations were normal and no visceromegaly was found. The chest roentgenogram showed a normal heart size and clear lung fields. The electrocardiogram was unremarkable. A second two-dimensional echocardiogram (see figures 1 to 3) showed the same 2 cm, non-pedicated mass, well demarcated, with evidence of tricuspid insufficiency by Doppler study (not quantitated; see figure 4). All chambers had a normal size. In view of the large size of the mass, the development of TV insufficiency, the persistent low-grade fever, and the pulmonary embolism, surgery was performed. A polypoid mass of about 2 cm in diameter was found adherent to the anterior TV leaflet with a central defect going through the leaflet with a central defect going through the leaflet itself. The mass and part of the anterior leaflet were excised and the TV



Figure 1. Apical four-chamber two-dimensional echocardiogram. The mass is seen on the right ventricular side of the TV. rv-right ventricle; lv-left ventricle; ra- right atrium, la- left atrium; tv- tricuspid valve; m- mass.

repaired. Pathologic examination of the mass demonstrated it to be a sterile vegetation. The patient completed six weeks of antibiotic treatment and has remained in good clinical condition since then, with clinically mild tricuspid insufficiency.



Figure 2. Apical four-chamber two-dimensional echocardiogram showing the mass on the right atrial side of the TV.

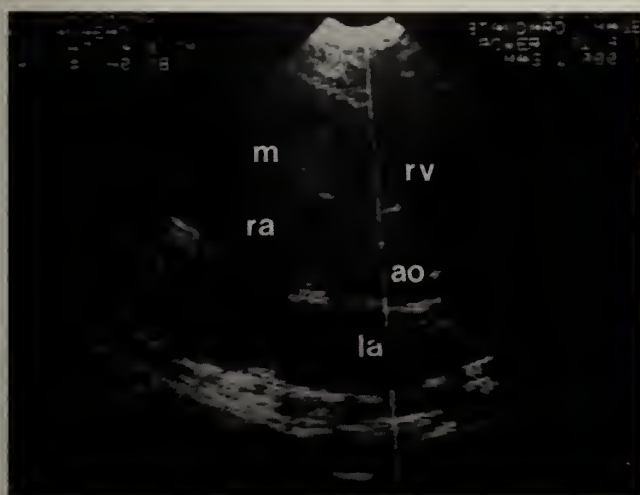


Figure 3. Parasternal short-axis view two-dimensional echocardiogram. m- mass.; rv- right ventricle; ao- aorta; la- left atrium; ra- right atrium.

Discussion

Although the clinical history was suggestive of TV endocarditis with a vegetation, the large size of the mass and its mobility pointed toward other possibilities, such as a tumor or a thrombus.

Atrial thrombi are usually non-homogeneous, immobile masses attached to the posterior atrial wall with a broad base,^{1, 2} but right atrial thrombi can also be mobile and frequently achieve a considerable size, creating the

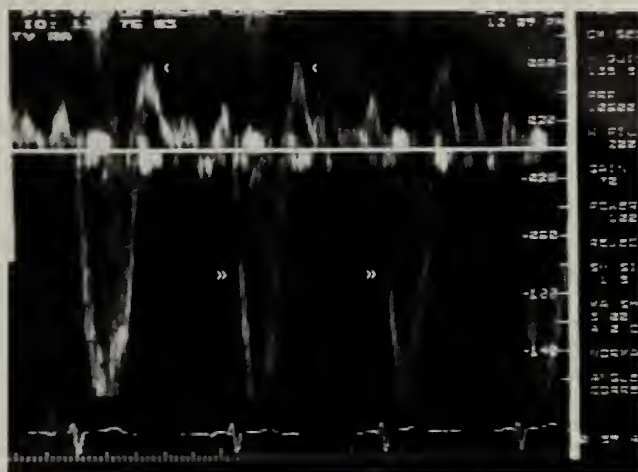


Figure 4. Doppler echocardiogram with the transducer at the apex and the sample volume in the right atrium (RA) showing blood flowing through the TV in diastole (single arrow) and into the RA in systole (double arrow).

possibility of massive pulmonary embolism and death.³ However, right atrial thrombi are rare and tend to occur with large atria, low cardiac output states or with relative stasis of blood (i.e. dilated cardiomyopathy), none of which were present in this patient.

Myxomas are the most common cardiac neoplasms and the right atrium is the second most common location for them.² They are usually pedunculated and tend to attach to the atrial septum. The large pedunculated myxomas are easy to diagnose by echocardiography, but the smaller non-pedunculated ones can be particularly difficult to visualize and may be confused with other intracardiac masses.³ Myxomas of the mitral valve have been reported, but not of the TV.^{4, 5} Typically they are very mobile and may traverse the atrioventricular (AV) valve, appearing in the ventricular side during diastole and in the atrium during systole. Sometimes an echo-free zone can be observed between the myxoma and the AV valve leaflets while the tumor traverses it, demonstrating that the leaflet itself is not involved with the tumor.² This was not present in our patient. Myxomas can be associated with fever, and are one of the many causes of fever of unknown origin.

The most important diagnostic possibility in our patient was a vegetation of the TV. Echocardiography can detect vegetations as small as 3 to 4mm in diameter.² They tend to be asymmetrical, involving one leaflet more than another, and can achieve a large size, particularly in the TV. In one particular series⁷ the mean maximal dimension of vegetations in the TV was 1.8 ± 0.8 cm. These large vegetations are mobile, flopping within the heart as in our patient. Although no blood cultures were available the most probable etiology of this vegetation was a *Staphylococcus aureus*. About 80% of the cases of right-sided endocarditis are caused by *S. aureus*; the remaining cases are largely caused by streptococcal, gram negative, fungal and culture-negative infections.⁸ At physical examination patients may have a murmur of tricuspid insufficiency that can be explained by interference in the closure of the TV leaflet by the vegetation or by destruction of the leaflets by the inflammatory process. In this particular patient the tricuspid insuffi-

ciency was produced by a perforation of the anterior TV leaflet and the vegetation, creating a tunnel-like orifice for the regurgitant jet. Pulmonary emboli may occur in more than 60% of cases of TV endocarditis,² particularly septic emboli. The early use of antibiotics in this cases could account for the absence of sepsis associated with the embolic episode.

In our case, the fever, the TV insufficiency, the pulmonary embolism and the echocardiographic features could be explained either by a myxoma or vegetation. It was the clinical history of intravenous drug use which favored a diagnosis of infective endocarditis.

Surgery was finally done due to the size of the mass, the occasional low-grade fever and the pulmonary embolism. In previously published series⁷ of patients with right-sided endocarditis almost 60% of the TV vegetations detected by 2D-Echo had a diameter greater than 1.0 cm. and of these about 33% required surgery. None of the patients with vegetations smaller than 1.0 cm. required surgery. In all cases the indications for surgery was persistent pyrexia. Peripheral embolism and the size of the mass itself are relative indications for surgery.

Conclusions

TV vegetations tend to be large and can be easily confused with tumors, particularly a myxoma, by echocardiographic imaging. Additional information from the history, the physical examination, and from ancillary tests is then required to arrive to a correct diagnosis.

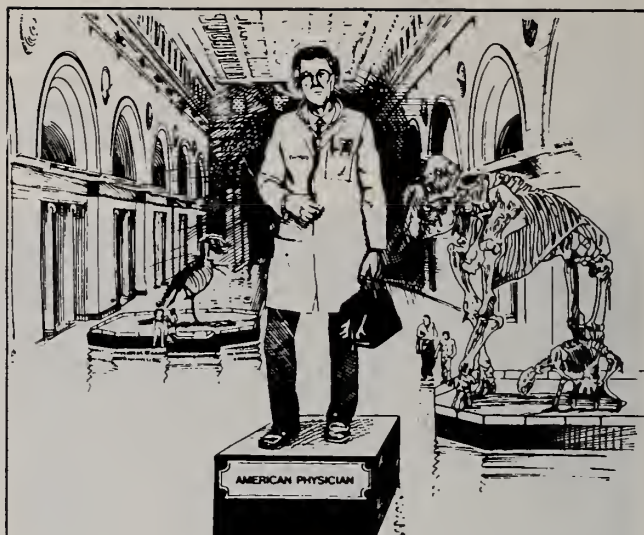
Persistent pyrexia is the most common indication for surgical treatment of TV endocarditis.

Resumen: El ecocardiograma bidimensional es un arma importante en el diagnóstico y diferenciación de masas intracardíacas, pero siempre debe ser incorporado dentro del cuadro clínico para un diagnóstico correcto.

Reportamos un paciente con una vegetación grande de la válvula tricúspide que simulada ser un tumor del lado derecho del corazón, especialmente un mixoma, en ecocardiografía bidimensional.

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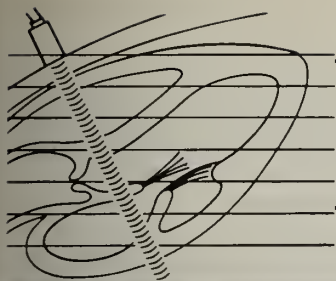
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ECHOCARDIOGRAPHY CASES

Mimicry and Errors in Echocardiography

Charles D. Johnson, MD, FACC

In spite of the echocardiographic literature having called attention to certain mimicking phenomena, errors continue to be committed in practicing and interpretive echocardiography.¹⁻⁷ This brief communication addresses one of many such misinterpretations, namely, that associated with intracardiac catheters. The following cases illustrate such pitfalls.

Case Reports

In case 1, figures 1A-1C, are M-mode echocardiograms from a woman with an acute myocardial infarction complicated by a ruptured ventricular septum.

In case 2, figure 2A is an M-mode trace and figures 2B and 2C, are two-dimensional (2-D) echocardiograms, parasternal short-axis (PSShAx) views, obtained on a young male drug abuser with suspected endocarditis.

All the echocardiograms were performed with Advanced Technology Laboratory (ATL) equipment, using a 3 MHz transducer.

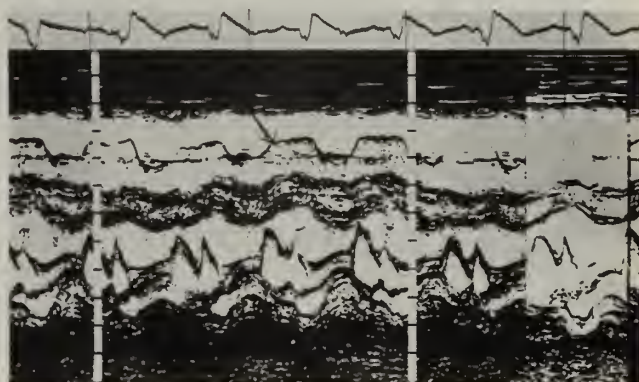


Figure 1B. Shows the Swan-Ganz catheter echo at a higher magnification.

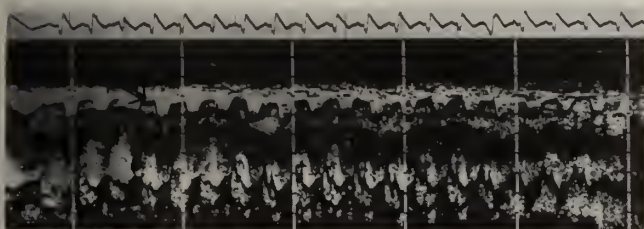


Figure 1A. M-mode scan of the heart. The Swan-Ganz catheter is visible in the right ventricle (RV) (arrow), anterior to the ventricular septum (VS), inducing a square-shaped diastolic curve, which mimics a normal tricuspid valve (TV). An electrocardiogram (ECG) is present at the top of the figure.

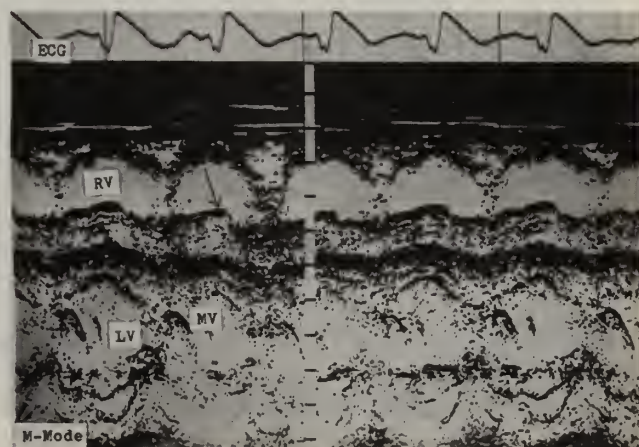


Figure 1C. The catheter echo is less discrete. MV-mitral valve. LV-left ventricle.



Figure 2A. M-mode trace of the heart. The catheter in the RV produced an anterior, flattened movement in diastole (arrow). LVPW - LV posterior wall.

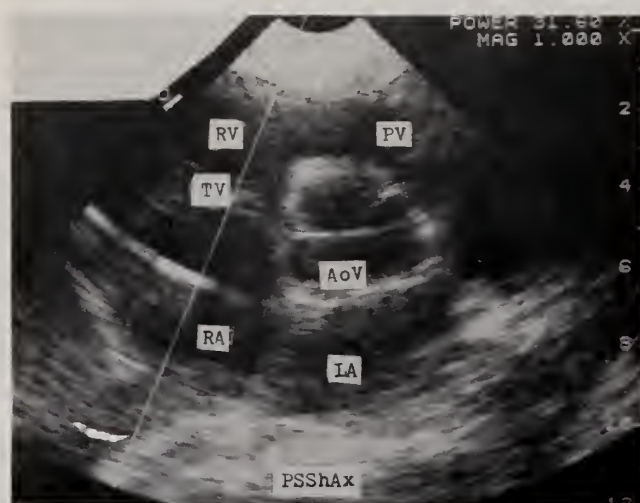


Figure 2B. Is a two-dimensional view at the base of the heart. A dense, tubular structure crosses the right atrium (RA), arrowed. PV-pulmonary valve. AoV - aortic valve. LA - left atrium.

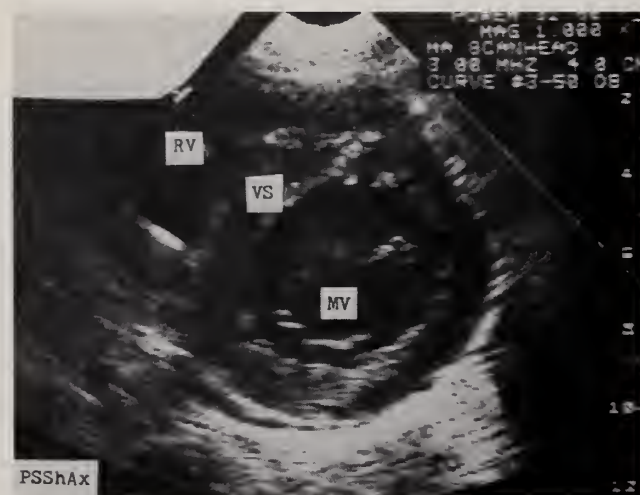


Figure 2C. The catheter entered the RV and is visualized as a dense tubular structure.

Results

Figures 1A-1C and 2A. In the right ventricle (RV) there was a heavy, curvilinear echo anterior to the ventricular septum (VS) with motion mimicking a tricuspid valve (TV), which represents the dense echo of a Swan-Ganz catheter. However, the anterior motion is flattened and the "C closure" is delayed. Even a posterior leaflet of the TV was suggested in some traces. The mitral valve (MV) was seen in the left ventricle (LV).

Figures 2B and 2C, at the base of the heart and at the MV level, respectively. A discrete round, linear, dense echo was visualized in the 2-D view of the right atrium (RA), representing a central venous catheter which had fallen into the heart. It was not observed in the RV outflow tract.

Discussion

Both M-mode and 2-D echocardiography have become a major cardiological diagnostic technique in recent years. In this same period, intracardiac therapeutic and diagnostic catheters have also assumed popularity.

Images of various cardiac catheters, positioned in the RA, the RV outflow tract and the pulmonary artery, including Swan-Ganz and pacing catheters, may be visualized on both M-mode and 2-D echocardiograms. If the interpreter of these studies fails to remember or consider this, these catheters may present diagnostic pitfalls, being misdiagnosed as various normal or pathological intracardiac structures.¹⁻⁷

Catheters may produce bright, linear, round or curvilinear echoes. Dense, shadowy reverberations occur behind a catheter (and the distorted TV), since it is a strong reflector of ultrasound. These reverberations, as a series of linear echoes, may be observed in the LV from a RV catheter. Catheter echoes are heavier, multiple and make a larger excursion than those of the TV. They are not usually as mobile as those from a vegetation. However, TV echoes may be prominent after ventricular septal rupture without a catheter, due to the left-to-right shunt, as observed in reported cases. Detection of a perforated pacing catheter is also possible with echocardiography.¹⁻⁷

Conditions which an intracardiac catheter may simulate are listed in table 1.

Table I

Conditions Which an Intracardiac Catheter May Mimic
Anterior leaflet of the tricuspid valve, or pulmonic valve; it may obscure the pulmonic valve.
Intracardiac masses, thrombi, tumors such as a myxoma; vegetations.
Ventricular septal hypertrophy, due to the catheter along the right side of the septum.
Ebstein's anomaly, from apparent late closure of the tricuspid valve.
A thickened anterior right ventricular wall.
Anterior pericardial effusion, or cardiac tamponade, because of the space between the catheter echo and the chest wall.
Dissection of the aortic root, because of the thick multilayered anterior aortic root.

Resumen: Este artículo trata sobre uno de muchos errores de interpretación diagnóstica ecocardiográfica, el cual consiste en catéteres intracardiacos que imitan varias estructuras patológicas y cardíacas.

Acknowledgement

All the echocardiograms illustrated in the paper were performed at the cardiac Noninvasive Laboratory of the University Hospital at the Puerto Rico Medical Center.

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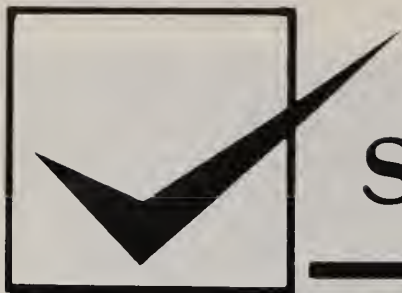
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SPECIAL ARTICLES

Common Prevalence of Coronary and Peripheral Vascular Disease*

Dr. Uwe Müller-Bühl**
Dr. Gotthard Schettler,**

Atherosclerotic involvement of the arterial wall in different body areas is a long-known and common autopsy observation. In the Framingham Study men with antecedent uncomplicated angina pectoris had an approximately threefold, and women a fivefold risk of claudication compared with the risk of their CHD-free cohorts. Subjects with claudication had an increased propensity to cardiovascular morbidity and mortality.¹ However, for the physician in hospital and practice settings, it is important to know immediately the probability of concomitant vascular diseases to decide on consecutive diagnostic and therapeutic steps.

Therefore a cross-sectional study was performed to evaluate the common prevalence of coronary artery disease (CAD) and peripheral vascular disease (PVD) using sensitive invasive and noninvasive diagnostic methods.

Between May 1983 and December 1985, 150 males with characteristic symptoms of intermittent claudication and verifiable PVD were included in the study after randomization. To determine the presence of CAD, dipyridamole-thallium scintigraphy was applied. Simultaneously, 150 males who had undergone coronary angiography because of suspected CAD, were randomized and recruited from the routine cardiac catheterization programme. Serious CAD was defined as a narrowing of the diameter of a major coronary vessel by 50% or more. PVD was assessed in these patients by the Doppler flow detector at rest and after treadmill exercise.

To all patients entering the study the established guidelines for assessment of atherogenic risk factors were applicable. Hyperlipoproteinaemia was presumed if patients received lipid lowering therapy or if blood lipids were above the recommended levels (Consensus Conference, Naples 1986): triglycerides 180 mg/dl, total cholesterol 200 mg/dl, LDL cholesterol 210 mg/dl.

Coexistence of Coronary and Peripheral Vascular Disease

Coronary artery disease was identified in about 50% of PVD patients, whereas about 20% of CAD patients had occlusive arterial disease to the lower limbs. Fig. 1 shows the classification of subjects into four groups. PVD occurred in patients with CAD, independent of age, while the prevalence of CAD increased with age in the PVD patient groups. No significant correlation existed between the clinical criteria for the degree of PVD (Doppler, painfree walking distance) and methods to estimate the severity of CAD (Gensini-Score).

Relations Between the Evaluated Cardiovascular Diseases and Risk Factors

Except for hyperlipoproteinaemia there was an overall trend of increased risk factors in the PVD patient group compared with CAD patients (Table 1). Patients with PVD were about five years older than subjects suffering from CAD. However, a significant influence of age on other risk factors was excluded by discriminate analysis. Triglyceride levels were not related to CAD, PVD or their combination. In contrast, the plasma levels of total cholesterol and LDL cholesterol were significantly higher, but HDL cholesterol and APO-A-I lower, in patients with CAD compared to the PVD groups (Table 2).

Conclusions

Populations studies in Finland and the United States have revealed symptoms of claudication in about 2.2% of men and 1.8% of women. The prevalence of CAD in a normal population is estimated at approximately 10%.² A number of investigations was performed to study the cardiac risk of occult and clinically evident CAD in patients scheduled for lower extremity revascularization. The frequency of CAD in these patients varied from 30 to 90%.³ The results of our study demonstrate that the frequency of concomitant disease depends on the kind of underlying arterial disease. Every second patient who joins the vascular laboratory with intermittent claudication is suffering from CAD. Conversely, the prevalence

*Reprinted from *Heart Beat, Journal of the International Society and Federation of Cardiology*, March 1988, p. 3-4

**Department of Medicine, University of Heidelberg, Heidelberg, FRG

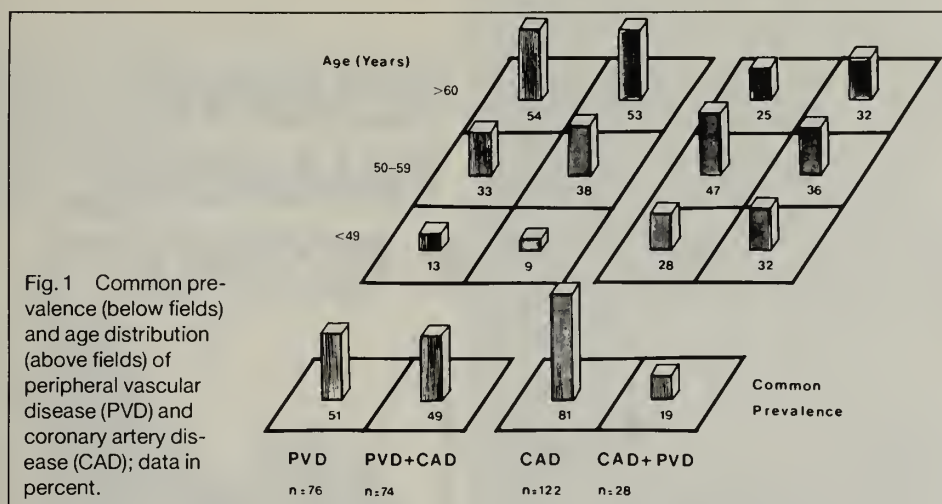


Table 1 Comparison of cardiovascular risk factors in patients with coronary and peripheral vascular disease; data in percent.

	PVD total n = 150	CAD total n = 150	p <	PVD n = 76	CAD n = 122	p <	PVD + CAD n = 74	CAD PVD n = 28	p <
Age	60	55	0.001	60	55	0.001	60	55.5	0.001
Hypertension	52.7	28.7	0.001	52.6	28.7	0.001	52.7	28.6	0.05
Diabetes	14.8	8.7	n.s.	14.5	9.0	n.s.	15.0	7.1	n.s.
Obesity	38.7	24.7	0.05	40.8	23.8	0.05	36.5	28.6	n.s.
Smoking total	79.3	54.0	0.001	84.2	46.7	0.001	74.3	85.7	n.s.
active	58.0	40.0		64.8	32.8		91.4	71.4	
other	21.3	14.0		19.7	13.9		23.0	14.3	
Hyperlipoproteinaemia	77.8	86.7	0.05	77.6	87.7	0.05	78.1	82.1	n.s.

Table 2 Comparison of plasma lipids and lipoprotein levels in patients with coronary and peripheral vascular disease (median).

	PVD total n = 150	CAD total n = 150	p <	PVD n = 76	CAD n = 122	p <	PVD + CAD n = 74	CAD PVD n = 28	p <
Triglycerides	177	183	n.s.	185	173	n.s.	176	189	n.s.
Total cholesterol	220	221	0.05	225	231	0.05	215	233	n.s.
HDL cholesterol	36	34	0.05	37	34	0.05	41	41	n.s.
LDL cholesterol	138	162	0.001	134	162	0.001	140	162	0.001
VLDL cholesterol	32	30	n.s.	35	30	n.s.	31	28	n.s.
APO A-I	159	140	0.05	158	141	0.05	159	145	n.s.
APO B	131	136	n.s.	134	133	n.s.	130	140	n.s.

of PVD in patients with angina pectoris is rarer and often masked by difficulty in achieving adequate exercise stress.

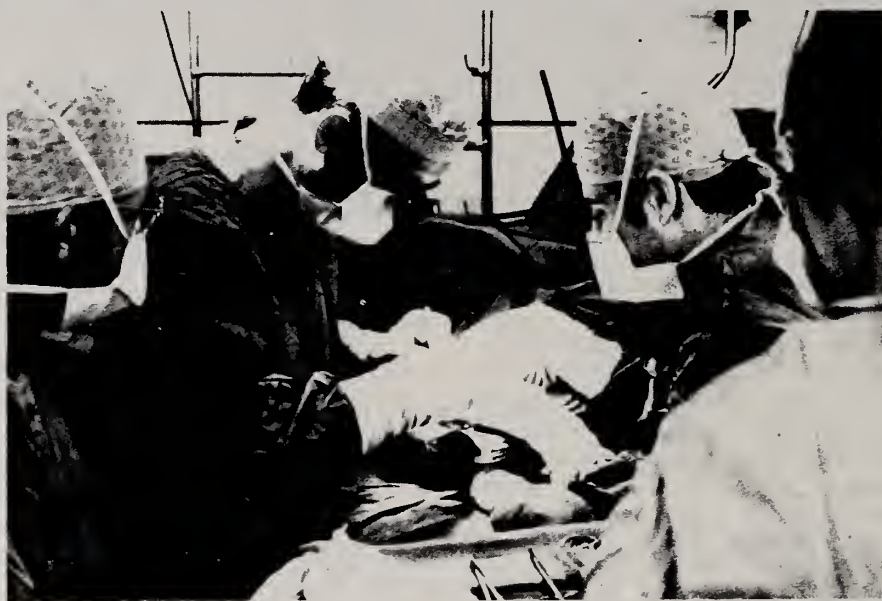
In conclusion, clinical assessment of coronary and peripheral circulation has been clearly improved in the last decades by modern invasive or noninvasive methods. Invasive procedures are more informative but limited at present by risks and costs. Using both invasive and non-invasive procedures in accordance with earlier autopsy findings and epidemiologic studies, we found considerable differences in the common prevalence of coronary and peripheral vascular disease, depending on clinically leading symptoms. Thus the problem of the co-existence of different arteriosclerotic involvement is more complex

than previously thought. A better insight into the natural course of arteriosclerosis and its underlying mechanisms may help to understand these findings.

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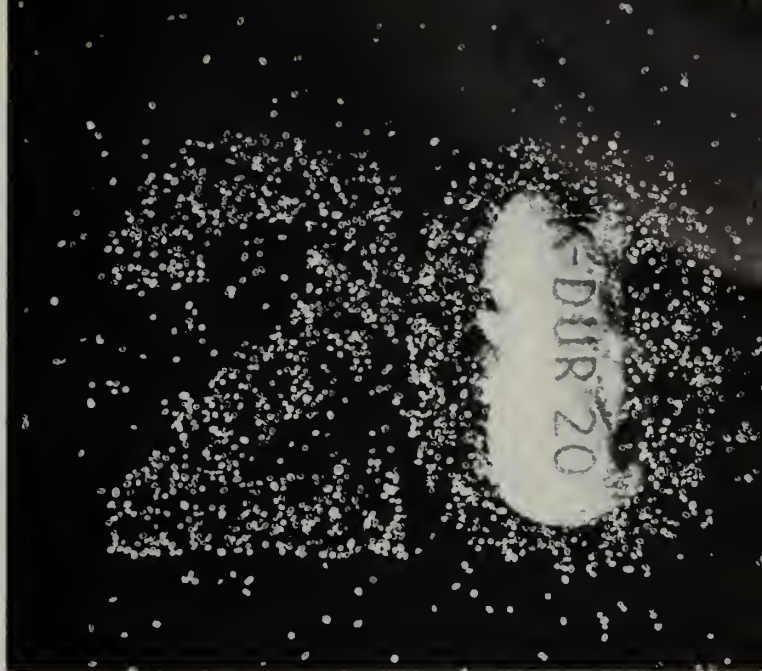
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CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

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WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

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Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS**.

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Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS, and OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS and WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS and WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:


1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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MEDICAL ASPECTS OF NUTRITION

Nutrient Interactions Involving Vitamins and Minerals*

John W. Erdman Jr., PhD.**
Angela G. Poneros-Schneider, M.S.**

While hundreds of interactions between nutrients are known to exist, the focus here will be on those nutrient interactions involving vitamins or minerals which are of potential importance to human nutrition. The term nutrient interaction implies that the amount of one component in the diet may affect the requirement and/or metabolism of other nutrients.

This article will address both positive and negative interactions of nutrients. Although many of these interactions occur normally and may be essential for proper human functions, others are potentially harmful. Adverse nutrient interactions can be of particular significance for those who are pregnant lactating, for infants or for the elderly. Also, consumers who self-prescribe megadoses of vitamins and minerals may have adverse interactions of nutrients, especially if they take excessively large amounts of single nutrient supplements. The American Medical Association (AMA) is generally concerned with intakes of vitamins at ten or more times the Recommended Dietary Allowances (RDA).¹ However, interactions of some minerals at levels lower than ten times the RDA are of potential concern.² Since most of the research studies in this area are performed under very defined conditions, specific levels at which interactions will occur are difficult to predict in mixed food systems.

Interactions among the nutrients often determine the bioavailability of these nutrients. Below are some definitions that relate to nutrient interactions.

Bioavailability is the efficiency with which a nutrient is available for absorption and utilization by the host.

Absorption is the uptake of a nutrient in the gastrointestinal (GI) tract and transfer into the body via the portal blood or lymphatic system.

Inhibition occurs when a substance impairs the

absorption and/or utilization of another nutrient. This may occur within the food by reaction with another compound which affects bioavailability or by competition. Competition is an antagonistic that can occur with structurally similar elements or compounds. It may occur at sites of absorption, utilization, storage or excretion. This interaction is of particular concern when one element/compound is in excess. Even essential dietary components, when taken at levels ten or more times the RDA, may cause deficiency signs of another competing nutrient.

Enhancement occurs when a substance promotes the absorption and/or utilization of another nutrient.

Positive Interactions

Two well-known positive interactions involving minerals and vitamins are given as examples below.

- **Iron** - Due to its chelating and reducing properties, ascorbic acid enhances the absorption of nonheme iron.³

By maintaining iron in the ferrous form (reduced), ascorbic acid increases the solubility of iron at intestinal pH. Additionally, ascorbic acid complexes strongly enough with iron to enhance iron solubility, but weakly enough to allow iron to be released to the intestinal cells. The absorption of heme iron, a highly bioavailable form of iron, is not affected by ascorbic acid. However, the bioavailability of both heme and nonheme iron is greatly enhanced by animal tissue in the diet.^{2, 4} The mechanism of this enhancement has not been clearly delineated.

- **Calcium** - Several dietary factors are thought to affect calcium bioavailability. Sugars, such as lactose, fructose, glucose and xylose, have been reported to enhance calcium uptake by the GI tract.⁵ The effect of dietary fat on calcium absorption is a controversial topic. Fatty acids have been shown to cause a decrease in calcium absorption due to the formation of calcium soaps in the GI tract; however, triglycerides appear to have no effect on calcium absorption.⁶ Other studies have shown that medium-chain triglycerides improve the absorption of calcium from infant formulas.⁵

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Negative Interactions

Of the many examples of negative interactions, most involve mineral interactions. Some examples of these interactions are given here.

● **Copper** - The copper-zinc competitive interaction is one of the most studied interactions in human nutrition. It is widely recognized that high intakes of supplementary zinc will depress circulating levels of copper and copper-containing enzymes, possibly by interfering with copper absorption.⁷ This interaction could lead to copper-deficiency anemia.⁸ Even a modest increase in dietary zinc in both man and laboratory animals can reduce copper absorption.² The negative effect of zinc on copper absorption has been used successfully to treat patients with Wilson's disease, a rare genetic disorder where persons absorb and accumulate abnormally high levels of copper.⁸ High levels of copper have also been shown to decrease zinc utilization, but the effect is small and probably not of practical importance.^{8, 9}

While vitamin C enhances the absorption of nonheme iron, its effect on copper is just the opposite. The reducing properties of ascorbic acid make copper less available for absorption. High levels of ascorbic acid can depress serum ceruloplasmin and serum copper levels and induce copper-deficiency anemia.¹⁰

Copper absorption and utilization has been shown by some studies to be affected by the amount of fructose in the diet.^{11, 12, 13, 14} Studies with rats fed diets deficient in copper with fructose or sucrose as the carbohydrate source have demonstrated that these sugars can exacerbate the severity of copper deficiency.^{12, 13, 14} The detrimental effect of sucrose appears to be related to its fructose moiety.¹³ This negative interaction of fructose with copper may be of potential concern. Due to the increasing proportion of fructose in the diets in the United States,¹⁵ the interaction of fructose with copper nutrition in humans needs to be further explored.

● **Calcium** - Phosphorus, protein, oxalate and phytate are frequently implicated in reducing calcium absorption. However, at the levels consumed by most Americans, these factors probably have either no effect or a relatively mild one. Conflicting reports appear in the literature concerning fiber's effect on calcium bioavailability. Early studies had suggested that high fiber intake may be a factor in calcium imbalance.⁵

Other research revealed that such imbalances appear initially in subjects consuming a high dietary fiber diet (greater than 30 grams per day), but the response is transient and is often followed by adaptation to the new diet.^{16, 17} Evidence exists to indicate that this same pattern of imbalance and subsequent adaptation of the subject may be true for other minerals as well.¹⁸

● **Zinc** - Phytic acid from cereal and legumes is a major contributor to reduced zinc bioavailability from those foods. This interaction is aggravated by calcium but may only be of significance to humans when dietary calcium intake is high. The formation of insoluble zinc-calcium-phytate complexes in the GI tract is believed to be one of the major mechanisms by which phytate reduces zinc bioavailability. Due to this synergistic effect of phytate and calcium on zinc absorption, the [phytate]

[calcium] / [zinc] ratio may be a useful indicator of zinc bioavailability.^{19, 20} Thus, caution should be exercised with the use of calcium supplements at a level much greater than the RDA if the diet is already high in phytic acid. Phytic acid has also been reported to be one of the factors in low iron bioavailability from cereals and legumes. However, phytic acid may not be the major inhibitor.²¹

An excess of dietary iron has been shown to reduce zinc absorption. The inhibition of zinc absorption by iron has been reported to occur at a 2:1 molar ratio of iron to zinc. Since the human diet usually contains about a 1:1 ratio, the antagonism by iron on zinc may only become significant in persons taking iron supplements. Also, infant diets with high iron: zinc ratios are of concern.²²

● **Iron** - Adverse effects of very high levels of zinc on iron bioavailability are widely recognized; however, more recent studies suggest that a more moderate intake of zinc from zinc-supplemented conventional diets or from therapeutic preparations can restrict the absorption and utilization of iron.²³

Several foods and food components have been shown to inhibit iron absorption. These include tea, coffee, eggs, wheat bran, some soy products and calcium/phosphate salts.² However, at normal intakes of these substances in the diet, iron status is unlikely to be compromised.

● **Vitamin A** - Both animal and human studies have shown that zinc deficiency results in a reduction in plasma vitamin A level despite diets adequate in vitamin A. The depressed plasma vitamin A apparently results from food- and growth-restriction factors and/or a reduction in protein synthesis which is associated with zinc deficiency.²⁴

When vitamin A intake is marginal, vitamin E is known to enhance vitamin A absorption and to have a sparing effect on body stores of vitamin A. Likewise, when vitamin E is deficient in the diet, vitamin A stores are especially susceptible to degradation. On the other hand, high levels of vitamin E may also affect vitamin A metabolism, but in a negative way. Excessive intake of vitamin E appears to inhibit B-carotene conversion to vitamin A in the rat.²⁵

Conclusions

Consumption of a variety of foods is unlikely to result in adverse nutrient interactions. However, negative interactions may occur when one consumes nontraditional or fad diets. Of most concern, though, is the growing use of high potency, single-nutrient supplements which may upset the normal absorption and utilization of other nutrients. The mechanisms of many of these interactions are not clearly understood at this time and considerable research efforts are needed in this area.

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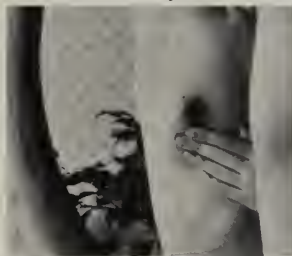
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CARTAS AL EDITOR

Certificado de Proficiencia vs Certificado de Asistencia en Resuscitación Cardiopulmonar

Miembros del Comité de Resuscitación Cardiopulmonar (RCP) de la Asociación Puertorriqueña del Corazón han expresado preocupación por el hecho que algunas facilidades de adiestramiento de CPR y algunos instructores certificados de RCP están otorgando "Certificados de Asistencia" a los cursos de resucitación cardiopulmonar básica (RCPB) en vez de ofrecer solamente "Certificado de Proficiencia". Preocupa también el hecho que el Tribunal Examinador de Médicos y los de otras profesiones aliadas a la salud están aceptando estos Certificados de Asistencia para cumplir con este requisito.

El Certificado de Proficiencia o Aprovechamiento indica que se ha completado satisfactoriamente el curso de Resuscitación Cardiopulmonar y que se demostró poseer los conocimientos y las destrezas necesarias para efectuar el procedimiento correctamente. En cambio el certificado de asistencia implica que el candidato no pudo completar satisfactoriamente con todas las normas o estas no fueron exigidas en el curso. En específico, no se hizo el trazado aceptable de un rescatador, que demuestra proficiencia en las destrezas de CPR.

A los profesionales de la salud, sobre todo a los médicos, se les debe exigir todas las destrezas de RCPB, un rescatador, dos rescatadores, infantes y tratamiento de obstrucción de vías respiratorias antes de entregarle un Certificado de Proficiencia. Los hospitales deben pedir como requisito de empleo para los profesionales de la salud un certificado de proficiencia en RCPB y a los médicos se les debe solicitar este certificado para poder renovar privilegios en la Facultad Médica y como parte de los requisitos de educación continuada para su registro cada 3 años.

Se ha creado un híbrido que es el certificado de asistencia y este debe desaparecer. Las nuevas normas de RCPB se han simplificado lo suficiente para que todos los profesionales de la salud puedan aprender y ejecutar las destrezas de RCPB. RCP desde el punto de vista educacional requiere unas destrezas que no son fáciles de ejecutar. A los candidatos para certificación, que no demues-

tren habilidad o tengan algún impedimento, el curso se le debe enseñar en más de una sesión, y a estos casos meritorios, se debe dar atención individual hasta lograr las destrezas requeridas para un Certificado de Proficiencia.

Llegó el tiempo de crear consciencia en los Comités de Educación Médica y en las Facultades Médicas de los Hospitales de Puerto Rico y además en el Tribunal Examinador de Médicos y los de las profesiones aliadas a la salud para que al otorgar privilegios o licencias para la práctica de una profesión se exija un certificado de proficiencia o aprovechamiento otorgado por la Asociación Puertorriqueña del Corazón u otra Institución certificadora reconocida.

Recomendamos que en el futuro se expidan solamente Certificado de Proficiencia. Los certificados de asistencia no se deben seguir otorgando a los profesionales de la salud y las instituciones no lo deben aceptar como evidencia de haber cumplido con el requisito de RCPB.

Francisco Jaume, MD, FACP
Comité de Resuscitación Cardiopulmonar
Asociación Puertorriqueña del Corazón

Las Primeras Doctoras en Medicina de Puerto Rico

He leído con interés esta reseña histórica escrita por la Dra. Norma I. Cruz sobre nuestras primeras siete doctoras en medicina.* Quiero señalar que la referencia que la autora hace a "la casa de huéspedes que había establecido Don Rafael Janer para mujeres estudiantes" no es del todo exacta.

Don Rafael Janer estableció una "Escuela-Casa Pensión" en la ciudad de Baltimore en el año 1901 con el propósito principal de servir como escuela preparatoria para los estudiantes puertorriqueños cuyos padres querían ofrecerles una educación en los Estados Unidos. Con ese nombre la anunciaba Don Rafael en el "Baltimore Sun" (famoso diario de esa ciudad) y en periódicos de Puerto Rico. De hecho, cuando sus estudiantes se referían a esta institución lo hacían llamándola "La Academia de Puerto Rico en Baltimore". Tan ésto es así, que en la Antología de Autores Puertorriqueños

*Boletín Asoc Med P R Abril, 1988

(Vol. III), cuya selección y estudio estuvo a cargo de Concha Meléndez, al ésta escribir unos datos biográficos sobre el cuentista puertorriqueño Angel M. Villamil incluye, entre otros, el siguiente, y cito: "Cursó su escuela elemental y superior en la Academia Puertorriqueña de Baltimore, Maryland, bajo el pedagogo Rafael Janer y se graduó de doctor en derecho de la National Law School, de Washington, D.C."¹ Es decir, que esta institución no era una sencilla "casa de huéspedes".

Es probable que, como escribe la Dra. Cruz, los requisitos impuestos por la Asociación Médica Americana tuvieran algo que ver con el cierre del "Women's Medical College" de Baltimore. Sin embargo, yo no creo que éste fuera ni el único ni el más importante factor. El informe del Dr. Flexner, presidente del Comité de la AMA que tuvo a su cargo la investigación de las escuelas de medicina que reclamaban dicho título en los Estados Unidos, se hizo público y se comenzó a aplicar en 1911, un año *después* de haber cerrado sus puertas la referida escuela. Además, con anterioridad a esta fecha, ya se venía comentando la crisis económica por la que atravesaba dicha institución y la reducida matrícula sobre la cual su solvencia financiera dependía. Estos también fueron factores determinantes en su cierre.

Como dato adicional, deseo apuntar que la Dra. Gatell fue la Medalla de Oro de su clase, siendo ella el primer estudiante puertorriqueño en obtener tan prestigioso honor en una institución americana.

No importa lo informado, la Dra. Cruz merece las más sinceras felicitaciones por su interés en rescatar de la historia los hechos a los cuales alude, interés que tiende a brillar por su ausencia en los miembros de la presente generación.

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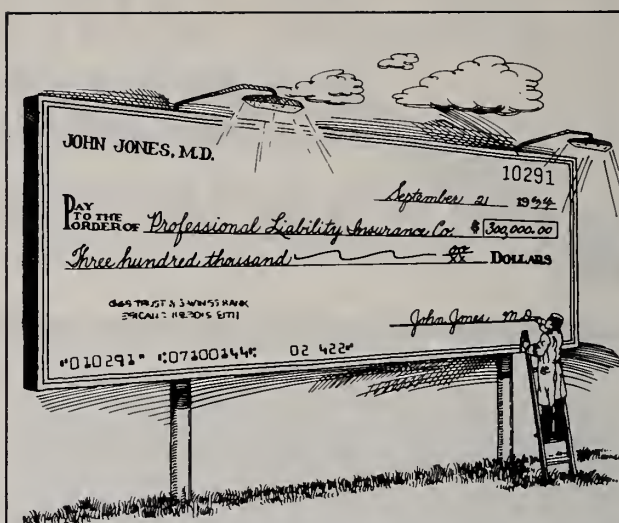
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Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

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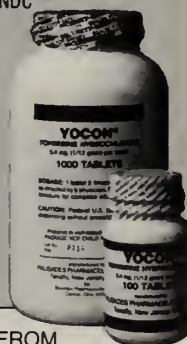
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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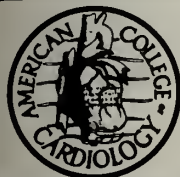
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The American College of Cardiology

ACUTE MI: STUDY LOOKS AT PATENCY RATES AFTER t-PA WITH CORONARY ANGIOPLASTY

For patients with acute myocardial infarction, a combined treatment of tissue plasminogen activator and either emergency or delayed coronary angioplasty can have positive results initially—that is, the patients receiving this combined treatment have high patency rates in the infarct-related artery at the time of hospital discharge. However, at long-term follow-up, the infarct-related artery shows the occurrence of restenosis and significant lesions.

Such are the findings that were presented by Charles A. Simonton, M.D., who is in the Division of Cardiology, Department of Medicine, Duke University, Durham, NC, at the American College of Cardiology meeting recently.

“Previous studies have shown that infarct-related vessels can be opened in approximately 75 percent of cases of acute myocardial infarction with tissue plasminogen activator (t-PA),” said Dr. Simonton. “However, the long-term patency rate had not been established using t-PA combined with coronary angioplasty. The purpose of this study was to combine the two treatments as an approach to achieving a long-term opening rate of the infarct artery in patients with severe heart attack,” says Dr. Simonton.

Dr. Simonton and his colleagues examined the opening rates for the infarct-related artery for 76 patients who received t-PA in combination with emergency coronary angioplasty, delayed coronary angioplasty, or coronary bypass surgery. “We performed follow-up angiography at one week and at a mean of seven months,” reported Dr. Simonton.

“Among the data collected, we found that at one week, patients who had received t-PA and emergency coronary angioplasty ($n=38$), 74 percent of infarct-related arteries were open with insignificant residual lesions. Yet at the

seven-month follow-up, these patients showed an overall open artery rate of 82 percent of which only 61 percent had insignificant stenosis.”

For patients who had delayed angioplasty following t-PA ($n=17$), 100 percent had open infarct-related arteries with insignificant stenosis at one week, but at seven months, 53 percent had developed significant stenosis.

“When we analyzed all of the data, we were able to draw the following conclusions,” said Dr. Simonton. “T-PA combined with emergency coronary angioplasty for acute myocardial infarction results in high long-term patency rate (82 percent) but is limited by significant stenosis in 39 percent of patients.”

“Secondly, t-PA and delayed coronary angioplasty has a high early success rate but a high rate of recurrent stenosis. Finally, t-PA without TPCA [coronary angioplasty] results in a high rate of significant stenosis both early and late but with continued long-term patency.”

Thus the approach of combining t-PA and either emergency or delayed coronary angioplasty opens occluded vessels early on, but later angiographs of heart attack patients show restenosis and significant persistent lesions.

Regarding further research, Dr. Simonton says, “We’ve been toying with the idea of trying to develop agents that will work in conjunction with t-PA for longer consistent patency rates. So our future direction is to look at thrombolytic agents and antiplatelet agents that will allow both a high early success rate with TPCA as well as success with avoiding restenosis in the long term”.

PRENATAL DIAGNOSIS OF INOPERABLE HEART DISEASE—A DEBATE

Does a prenatal diagnosis of inoperable heart disease justify terminating pregnancy?

Charles F. Kleinman, M.D., Professor of Pediatrics and Director of Pediatric Cardiology at Yale University, and Peter Lang, M.D., Associate in Cardiology at Children’s Hospital in Boston, MA, debated this issue at ACC ’88 in Atlanta recently.

Protagonist

Dr. Kleinman: First, we need to define what we mean by operable and inoperable. Yes, operations for hypoplastic left heart syndrome and heart transplants are feasible. But until there is any long-term follow-up, we can only look at these procedures as extremely innovative, bordering on research.

We must look at the fetus as a patient as a whole, not as an isolated organ. The question is: Is the patient operable?

For example, about 20 percent of the patients we see have heart lesions that may be operable. However, these babies are extremely swollen and are undergoing heart failure in utero. They have invariably died, no matter what sort of aggressive therapy has been afforded them.

For a mother to continue with such a pregnancy places her at potential risk for hypertension, in addition to a rather large cesarean incision that may result in future infertility.

Many times parents of these unborn children are asked to sign permission forms for very aggressive types of surgery when they themselves are under tremendous emotional stress. Although a mother is virtually always a strong advocate for her fetus, she is also concerned with the quality of life—as well as the survival—of her child.

It is our responsibility as physicians, therefore, to ensure that parents of such children are presented with a balanced view of the situation before any decisions are made. We should not allow our excitement about promising treatments to overwhelm the parents' considerations of what is best for them, their family and their fetus.

Antagonist

Dr. Lang: Our profound uncertainty as to the outcome of children born with very severe forms of congenital heart disease may be, in most cases, reason enough not to terminate pregnancy.

Our current understanding of cardiopulmonary physiology, allows us to manipulate the anatomy in such a way that children, even with the most severe forms of heart disease, can survive, grow and develop in near-normal fashion. For this to happen, an individual needs one well-functioning ventricular chamber. It is exceedingly unlikely that a child without such a chamber will survive gestation. Therefore almost all fetuses that survive to term have the potential for long-term survival. This includes children with hypoplastic left heart syndrome. There are currently several forms of congenital heart disease that have equally poor, if not worse, long-term prognosis than hypoplastic left heart syndrome. Yet, people don't think twice about performing palliative surgery in these cases.

No doubt there are instances of fetuses in utero where evidence of ventricular failure suggests a poor outcome. But they are clearly a very small minority. Termination of pregnancy in these situations is clearly justified.

Finally, the belief that we, as physicians, can present the diagnostic and prognostic data to parents in an objective, neutral fashion, is doubtful. When we discuss such situations, we cannot help but bring our personal biases into the discussion. This is a tremendous burden on all of us; it becomes unfair to place the burden of what to do on the parents.

shots in infancy showed no neurologic deficits when examined six to seven years later, a new study has found.

Published in the June issue of *Pediatrics*, the study evaluated 16 children who had convulsions or unresponsive episodes following DTP administration. The researchers concluded that it "is unlikely that such reactions lead to significant neurologic impairment."

"All of the children were described by their parents to be in good health, and all were considered to be doing well in school," the researchers, from the University of California, Los Angeles; Kaiser Permanente Medical Group, Los Angeles; and the Food and Drug Administration, wrote.

"The neurologic evaluation results of all of these children were considered to be normal with the exception of four minor abnormalities which we consider to be insignificant," they said. The researchers did not believe the abnormalities to be important; no child was currently undergoing neurologic care.

This study followed-up on a study of adverse reactions to 15,752 DTP shots given in 1978 and 1979 to Los Angeles children, 18 of whom had reactions within 24 hours of vaccine administration. Nine children had convulsions; nine had pale, unresponsive episodes. No child died or experienced a serious neurologic reaction. Sixteen children were evaluated for this follow-up study to determine any evidence of neurologic damage.

The authors concluded: "There is no evidence that any of these 16 children suffered any serious neurologic damage as a result of either convulsions or hypotonic-hyporesponsive episodes which were temporally associated with their prior DTP immunizations."

All the children's IQ scores were normal, although verbal IQ scores were low. The researchers attributed this to the proportion of bilingual children in this sample.

FETAL THERAPY: ETHICAL, MORAL DILEMMAS

When a woman neglects to have fetal intervention therapy, though it may save her fetus from irrevocable harm, she may actually be unaware of available treatments, says the American Academy of Pediatrics (AAP).

In a policy statement published in the June issue of *Pediatrics*, the AAP's Committee on Bioethics asserts that many fetal therapies—such as cesarean section for placenta previa and intrauterine transfusion for severe Rh blood type incompatibility—are standard practices of proven efficacy.

Other interventions, such a cesarean delivery for fetal distress, are routine practices but involve more ambiguous decisions. Still other practices are considered research procedures and are not standard medical practices.

In unusual cases, when a woman refuses treatment, the Committee writes, it places a moral burden on the physician. According to the Committee, physicians might consider actively opposing the woman's choice when: 1) there is substantial likelihood that the fetus will



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REACTIONS TO DTP SHOTS: CHILDREN NORMAL AT FOLLOW-UP

Sixteen children in Los Angeles who had adverse reactions to their DTP (diphtheria-tetanus-pertussis)

suffer irrevocable harm without the intervention, 2) the intervention is clearly appropriate and will likely be efficacious, and 3) the risk to the woman is low. The physician might try to persuade the woman to consent to treatment in these cases, or consult a hospital ethics committee.

Norman Fost, M.D., chairman of the Committee on Bioethics, explains that cases where women refuse treatment for their fetuses are rare. It's more likely, he says, that a woman is unaware of available treatment.

However, the physicians and the entire health care team should assist the parents in making an informed decision concerning therapy for their fetus, the Committee states. In addition, they should be generally supportive and available to the family, whatever the choice.

The most appropriate treatment comes from a team of professionals and balances the best interest of the fetus with potential risks to the woman, the Committee writes.

Pregnant women and their fetuses are increasingly viewed as two treatable patients, the Committee says. With recent advances in perinatal medicine, the fetus is less surrounded in mystery and more accessible to treatment in utero. This has, however, created a variety of ethical questions, such as to whom a physician is primarily responsible: the mother or her fetus.

The Committee says that women almost always are willing to undergo self-sacrifice to benefit their fetuses. "A woman who becomes pregnant and voluntarily chooses to go to term has a moral responsibility to undertake certain risks," asserts Dr. Fost.

These decisions also involve the woman's personal autonomy and bodily integrity because all therapeutic interventions on behalf of a fetus affect the woman and require her direct participation.

AAP SAYS SCHOOLS SHOULD TEACH AIDS EDUCATION K-12

"The nation's schools should immediately initiate AIDS education programs as part of a comprehensive health education plan," says a new statement by the American Academy of Pediatrics (AAP), stressing the need for candid emphasis in later grades.

The statement, issued by the AAP's Committee on School Health and published in *AAP News*, advocates AIDS education in kindergarten through twelfth grade.

Although the Committee acknowledges that abstinence is the safest method of prevention, it realizes "not all students will remain abstinent or be able to ensure that their sexual partners are uninfected." The Committee urges including discussion of appropriate contraceptive methods—condoms and spermicide—as part of the education curriculum.

The AAP's age-appropriate guidelines are:

- From kindergarten to third grade, concepts in disease and health should be taught, including the role of microorganisms and the importance of cleanliness in maintaining a healthy body. The role of

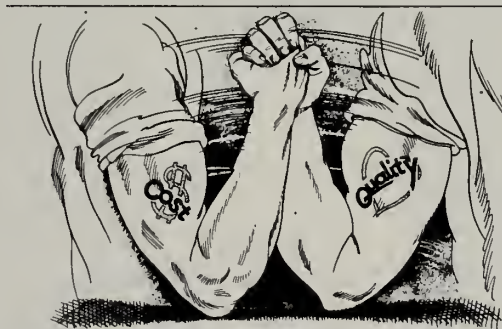
health professionals in preventing and treating illness in the family should be introduced.

- In fourth through sixth grade, the nature of AIDS and methods of transmission should be discussed, as well as concepts involving the control of body fluids. Myths about insects and the casual spread of AIDS should be dispelled.
- School children in grades seven through twelve begin to engage in behavior that may increase the risk of HIV infection. In this group, the curriculum needs to be most intense. Professional health educators should be utilized in these later grades.

The program should include: the spectrum and history of AIDS, the relationship between AIDS and the human immune system, the transmission of AIDS, prevention and treatment of AIDS, and the social and psychological aspects of AIDS.

In the later grades, the Committee urges candid discussion of all aspects of sexual transmission in an age-appropriate and culturally-sensitive fashion. "Curricula should emphasize an understanding of the psychological problems of families with children or other members who have AIDS, a knowledge of alternate lifestyles, special cultural sensitivities, civil rights and testing issues," the statement says.

"Since no vaccine or cure is available, education offers a reasonable approach to prevention," the Committee says. It also recommends that schools form health advisory committees to help develop and supervise the education programs.



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Oh, there is one thing, though.

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ROSALYN P. STERLING-SCOTT, M.D.

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Keep the Dream Alive





STUDY: EARLY EVALUATIONS OF MRI POOR IN QUALITY

Early research on the diagnostic efficacy of magnetic resonance imaging (MRI) is rife with poor methodology, suggesting "a new imaging modality that provides better pictures tends to become the diagnostic modality of choice without objective data to support its use," says a report in JAMA.

The study, by Lawton S. Cooper, MD, MPH, now with the University of Rochester, NY, and colleagues, reviewed 54 reports on MRI's diagnostic efficacy published from 1980 to 1984. It used 10 commonly accepted research methodology criteria, including evidence of research planning, appropriate data presentation and use of terms, and presentation of a "gold standard" against which to assess results.

"In the four years after MRI's first clinical evaluation, research on the diagnostic efficacy of this modality was limited to descriptive studies. No studies were identified that could be called high-quality assessments by contemporary criteria of research methodology," the authors say. Without such data, they say, "a new imaging modality that provides better pictures tends to become the diagnostic modality of choice without objective data to support its use. Once this happens, it is difficult to change utilization patterns with even the most scientifically conducted evaluation of diagnostic efficiency."

The terms sensitivity, specificity, false-positive or false-negative, accuracy and predictive values were used infrequently and many times inappropriately, the study says. Actual calculation of data for these terms was inconsistent, and a "gold standard" comparison with results of an independent procedure, such as surgical or autopsy findings, was presented in just 22 percent of the reports. In addition, "only one evaluation clearly described a prospective study design, although 11 evaluations apparently were planned in advance. Not one evaluation contained an appropriate statistical analysis of the distributions of quantitative readings, 'blinded' image readers to diagnosis or other test results, measured

observer error, or randomized the order of magnetic resonance imaging and other imaging procedures."

The authors attempt several explanations for these findings but find none acceptable. For example, they find no reason to believe "that the shortage of scientific quality was a reflection of differences in discipline of the investigators or unusually stringent criteria of research methodology."

They also reject the argument that because MRI is a new clinical technology, "a certain amount of clinical experience in descriptive studies must be obtained before proper evaluations can be reasonably performed." They say the research they reviewed was performed by a small number of researchers in a few institutions, "yet we also noted that during the 4 1/2-year study there was no improvement in the quality of the investigations, as might be expected if there were a progression from simple descriptive to more rigorous evaluative investigations." In short, "each of the 54 articles was apparently written and published to illustrate the diagnostic usefulness of the procedure," they say.

"We conclude that health care professionals paying for expensive innovative diagnostic technology should demand better research on diagnostic efficacy," the authors say. "As evaluations of diagnostic efficacy, these studies are of poor quality... Proper quantitative methods do need to be used in the evaluation of new technologies."

Considering the up to \$2 million cost of an MRI, the study's conclusions "raise serious doubts about whether limited resources are being wisely used, at least from the perspective of improved clarity of diagnosis or patient outcome," Samuel B. Sheps, MD, of the University of British Columbia, Vancouver, says in an accompanying editorial.

"There is no question that a fundamental problem has been the technological imperative in which clinicians (and in turn others) subscribe to the belief that increasing sophistication of technique or precision of results leads inevitably to or represents better health care," he writes. "While this is undoubtedly true in some cases... it remains critical that such improvement be demonstrated and not rest simply on the ideology of technological advance."

JAMA June 10, 1988

RECOMBINANT DNA-DERIVED HORMONE MAY HELP TREAT INFERTILITY: STUDY

A genetically engineered version of a human hormone that induces ovulation appears to be biologically identical to the natural hormone and may provide superior treatment for many female and male fertility problems, says a study in JAMA.

The substance, recombinant DNA-human luteinizing

hormone (rechLH), was produced by cultures of mammalian cells, into whose genes were spliced genes for the two subunits of human luteinizing hormone. The authors, James A. Simon, MD, of the Eastern Virginia Medical School, Norfolk, Va., and colleagues report that the product of this gene splicing technique appears biologically and immunologically identical to the natural human hormone that induces ovulation.

Along with another hormone that causes ovarian follicles to grow and mature prior to ovulation, luteinizing hormone is now extracted from human pituitary glands and from the urine of postmenopausal women. This impure preparation is used to treat infertility caused by hormonal abnormalities in both women and men. The availability of a pure, commercially produced, recombinant DNA-derived hormone promises to bring several therapeutic advantages to infertility practice, including a steadier supply of the hormone and a greater reliability of product potency, the authors say. In addition, its availability in a pure form that can be administered without other hormones would improve the flexibility of individualized patient management, they report.

Some of the infertility problems now treated with the gonad stimulating hormones include ovulatory disorders, endocrine disorders causing early pregnancy wastage, and, in men, androgen-deficient problems of libido and hormone-related failure to produce sperm. The hormones have also played a key role in vitro fertilization for sterility caused by damaged fallopian tubes, the authors report.

The hormone has not yet been tested on humans, but studies with rats and monkeys have shown that the effects of the rechLH preparation are virtually identical to the effects of the natural hormones, obtained from urine and pituitary glands, in triggering ovulation and supporting the function of the corpus luteum, a small glandular mass that plays a vital role in the first stage of pregnancy. Production of the male hormone testosterone in rats treated with rechLH was indistinguishable from production induced with natural hormones. The authors say that chemical analysis is needed to determine whether the molecular structure of the hormone is identical to the structure of the naturally occurring substance, and that clinical trials will be required to determine optimal use of the hormone and to assess whether it can cause immune or allergic reactions.

RechLH may have a major advantage over a similar hormone used to induce ovulation. In the body, the hormone, human chorionic gonadotropin, has a half-life of 10 hours compared to the 50-minute half-life of rechLH. The authors believe that use of the shorter-lived rechLH will reduce the frequency of multiple pregnancies that often result in patients treated with fertility hormones. Because reaction to rechLH may mimic the normal cycle more closely than the hormone mixture used now, the authors believe pure rechLH may achieve better timing in the development of the ovum, leading to better embryo quality.

The study was sponsored in part by an academic/corporate agreement between Serono Laboratories Inc., in Randolph, Mass., which produced the recombinant DNA-derived hormone, and the Eastern Virginia

Medical Authority, the authors say.

In an accompanying editorial, Alan H. DeCherney, MD, of Yale University School of Medicine, New Haven, Conn., says the authors' work on rechLH has opened up exciting possibilities in the rapidly growing field of ovulation induction, not only because of the potential for increased availability and quality control of the product, but also because it greatly expands therapeutic possibilities by increasing flexibility in treatments to induce ovulation. "Their work illustrates beautifully how the marriage of new technology and well-conceived and executed scientific experimentation and validation results in clinical realities that improve the quality of life," DeCherney says. "Read from a narrow perspective, this article merely documents the potential use of rechLH as a pharmacologic agent; but read with a wider vision, it illustrates the importance of basic science developments in the practice of modern-day medicine."

JAMA June 10, 1988

SYRUP OF IPECAC FOR CHILDHOOD POISONINGS

Syrup of ipecac is often used to induce vomiting when children ingest poison in the home, but reports in June's *American Journal of Disease of Children* (AJDC) suggest many more parents should have this medication on hand in case of such emergencies. Physicians could help by regularly dispensing ipecac in the course of pediatric care, say Michael H. Malloy, MD, MSc, and George G. Rhoads, MD, MPH, of the National Institute of Child Health and Human Development, Bethesda, Md. The authors' national survey data indicate that while 88 percent of respondents from households with young children had heard of poison control centers and 70 percent had the phone number of such a center, only 25 percent (9 percent for blacks and Hispanics) had ipecac syrup in the home. Seeking possible reasons for this, the authors interviewed 45 Washington, DC-area doctors and found that while most told their patients about poison control and believed parents should have ipecac in the house, only 7 percent actually dispensed it. "By incorporating the distribution of ipecac directly into pediatric care, it should be possible to place it in the homes and consciousness of most American Parents in a relatively few years," the authors say. A related *AJDC* article and two editorials echo this view. But another article, by H. Juhling McClung, MD, of the Columbus, Ohio, Children's Hospital, and colleagues, cautions that ipecac's "ready availability also provides the potential for child abuse and self-induced (vomiting)."

CHOLESTEROL-LOWERING DRUG MAY EXACERBATE PSORIASIS IN SOME PATIENTS

The promising lipid-lowering drug gemfibrozil, which decreases production of very-low-density lipoprotein

triglycerides and increases high-density lipoprotein cholesterol levels, may provoke or exacerbate psoriasis in some patients, a letter in June's *Archives of Dermatology* reports. David A. Fisher, MD, of the University of California-San Francisco, and colleagues describe a 64-year-old woman who noticed a generalized outbreak of psoriasis about two weeks after being placed on gemfibrozil therapy because of elevated low-density lipoprotein and cholesterol levels. The woman had reported a pre-existing rash characteristic of psoriasis, but her symptoms worsened significantly after she began taking the drug, the letter says. The problem cleared almost entirely after she was taken off gemfibrozil and treated with topical medication, the authors report, but she suffered a pronounced psoriasis flare-up when later placed on gemfibrozil again. Although an assortment of drugs are known to cause or exacerbate psoriasis and certain cholesterol-lowering agents have been associated with skin rash, there are no previous reports linking gemfibrozil to psoriasis, the letter says. "This case provides evidence that gemfibrozil should now be added to the list of medications that can provoke or exacerbate psoriasis," they recommend.

BREAST CANCER TREATMENT PRACTICES CHANGING: STUDY

A study in JAMA indicates a marked shift in recent years toward breast-conserving surgery for women with localized breast cancer, but suggests many such women—especially those over age 65—may not receive important follow-up radiation therapy.

Authors Bruce A. Mann, MD, of the University of New Mexico School of Medicine, Albuquerque, and colleagues acknowledge that their data are limited to New Mexico and suggest further studies from other states to confirm their findings. However, they say, their data suggest "that an unanticipated consequences of this rapid change (in surgical approach) might be a less-than-optimal application of breast-conserving surgery, with some patients not undergoing the breast-conserving procedure in combination with radiotherapy." This "may prove to be a deleterious consequence of this change in surgical management (of breast cancer)."

Surgeons have long debated the best way to treat breast cancer, which strikes one woman in 11. Clinical trials conducted during the 1970s and 1980s showed that for localized malignancies, breast-conserving surgery ("lumpectomy") in combination with radiation therapy was at least as effective as more radical surgical procedures (radical or modified mastectomy). But while these studies were widely reported in both the scientific and lay literature as reflecting changing attitudes about breast cancer surgery, the degree to which they translated into clinical practice has been unclear, the authors say.

The study reviewed data from the New Mexico Tumor Registry on women diagnosed with primary breast cancer from 1969, analyzing a total of nearly 6,000 cases. After

1980, it says, the proportion of women undergoing breast-conserving surgery for local-stage cancer increased from 6 to 25 percent. Women under age 50 and over age 80 were most likely to undergo breast-conserving surgery.

As further evidence of the shift in the surgical approach to localized breast cancer, the researchers note that most surgeons performing breast cancer operations had not performed a breast-conserving procedure prior to 1981, but had used the procedure at least once between 1981 and 1985. "Nearly all surgeons in the state who were performing operations for breast cancer changed their surgical approach," they say.

Because breast-conservative surgery is considered most effective when combined with radiation therapy, the authors also reviewed registry data for documented radiotherapy follow-up. Such follow-up could not be confirmed for 26 percent of patients under age 65 or for 56 percent of women aged 65 and older. Data collection problems might explain some of this, the authors say, but this still "would not explain the clear changes with age in the proportion of women not undergoing radiotherapy after breast-conserving surgery. Thus, our data suggest that some patients either were not offered radiotherapy or refused such therapy when it was offered. Some physicians may have considered breast-conserving surgery without radiotherapy to be adequate treatment."

The failure to follow breast-conserving surgery with radiotherapy would represent an important example of the "gap" between the latest in medical science and the reality of clinical practice that some researchers have noted, the study says.

"In the case of breast-conserving surgery, the gap arises from the optimal application of a new treatment in controlled clinical trials vs the subsequent, less optimal application in routine patient care," the researchers write. "Studies similar to ours, using tumor registry data from other areas of the country, would be useful to confirm this gap for breast cancer so that corrective measures may be undertaken."

JAMA June 17, 1988

STUDY FINDS VASODILATORS MAY PROLONG LIFE OF HEART FAILURE PATIENTS

Blood vessel-dilating drugs can relieve symptoms in heart failure patients, and one group of vasodilators may also prolong their life, says a study in JAMA.

Although the relative efficacy of different vasodilator agents has not been well established, they have been widely used along with other drugs to treat chronic congestive heart failure (CHF), which affects more than 2 million Americans and causes 200,000 deaths each year, say the authors, Cynthia D. Mulrow, MD, MSc, of The University of Texas Health Science Center at San Antonio, and colleagues.

In an analysis of 28 double-blinded, placebo-controlled trials, the authors found that "All vasodilator agents

except hydralazine hydrochloride were associated with improvements in functional status." However, only angiotensin converting-enzyme (ACE) inhibitors were associated with a decrease in mortality. ACE inhibitors work by blocking the formation of a substance in the bloodstream that constricts blood vessels. By widening blood vessels, vasodilators reduce the heart's workload, which increases the patient's ability to function, reduces symptoms and, at least in the case of ACE inhibitors, apparently decreases mortality.

However, in an accompanying editorial, Jay N. Cohn, MD and Thomas S. Rector, PhD, of the University of Minnesota Medical School, Minneapolis, say an analysis of the survival curves in the largest single trial with the longest follow-up period examined by the authors suggests that two other vasodilators—hydralazine and isosorbide dinitrate—used together may also reduce mortality. Only large-scale clinical trials will be able to answer the question of which vasodilator regimen should be used for which patients, the editorial says. In any event, the evidence now suggests that CHF patients should also be treated with vasodilators. "By prescribing an angiotensin converting-enzyme inhibitor, hydralazine and isosorbide dinitrate, or some combination of these drugs, the physician is assuring the patient a high likelihood of a beneficial effect," Cohn and Rector conclude.

JAMA June 17, 1988

ALTITUDE, LOW BIRTH WEIGHT AND INFANT MORTALITY

Birth weight is known to decrease at higher altitude due to intrauterine growth retardation, but this doesn't necessarily translate into higher infant mortality, a study in JAMA says. Studying 1979-1982 Colorado vital statistics, Cynthia Unger, MA, of the University of Colorado at Denver, and colleagues found the frequency of low-birth-weight infants at the highest altitudes in the state (over 9,000 feet) was double that at the lowest (3,000-4,999 feet). But while low birth weight raised mortality risk, the mortality risk of low birth weight was actually decreased at high compared with low altitudes, resulting in similar infant mortality rates statewide, the authors say. They note a sharp statewide reduction in infant mortality from 1973 to 1982, mainly due to lower mortality risk for premature low-birth-weight infants. "This reduction, particularly pronounced at high altitude, might have been due to better identification and transport of high-risk pregnancies to hospitals with tertiary neonatal treatment centers," they say.

JAMA June 17, 1988

IMMUNOAUGMENTATIVE THERAPY UNACCEPTABLE FOR CANCER: AMA PANEL

Immunoaugmentative therapy (IAT), injections of

protein fractions isolated from necrotic tumors and blood pooled from cancer patients and healthy donors, is an unacceptable cancer "treatment," an AMA science study panel says in JAMA. Seventy-three percent of the 27-member Diagnostic and Therapeutic Technology Assessment panel found IAT, offered by a clinic in the Bahamas, "unacceptable" in terms of safety; 23 percent found it "indeterminate." In terms of effectiveness, 59 percent called IAT unacceptable, 22 percent investigational and 19 percent "indeterminate." "The known risks posed to recipients of this 'treatment' clearly outweigh the unproved claims of effectiveness even for this often desperately ill population of patients," the report says. "The scientific evidence to date, as well as the history of IAT, will allow no other conclusion than that IAT is unequivocally dangerous to its patients and of no proved value as a treatment for cancer."

JAMA June 17, 1988

PREGNANCY, BREAST FEEDING AND MULTIPLE SCLEROSIS

Several studies suggest that pregnant women with multiple sclerosis (MS) are likely to see their symptoms worsen after childbirth, perhaps due to hormonal effects on the immune system. But breast-feeding does not appear to alter this risk of MS exacerbations, a study in JAMA says. The report by Lorene M. Nelson, MS, now with the University of Washington, Seattle, and colleagues, involved interviews with 435 women with MS regarding pregnancy and breast-feeding history; 191 pregnancies were analyzed. Exacerbations of symptoms were more than three times as likely during the nine months following childbirth as during pregnancy itself. Breast-feeding did not appear to affect the risk or timing of postpartum exacerbations. "Specific counseling regarding the advisability of breast-feeding should be based on practical considerations rather than on concern about a worsening in disease related specifically to breast-feeding," the study concludes.

JAMA June 17, 1988

RISK FACTORS FOR ADOLESCENT SUICIDE

Adolescent suicide victims are much more likely to have firearms available in their homes than other youth at risk for suicide, a study in June's *Archives of General Psychiatry* suggests. The report, by David A. Brent, MD, of the Western Psychiatric Institute and Clinic, Pittsburgh, and colleagues, studied 27 adolescent suicide victims and a comparable group of 56 suicidal psychiatric inpatients. Four risk factors were more prevalent among the suicide victims: diagnosis of bipolar disorder (manic-depression); affective disorder (a broad group of depression problems) with other psychiatric diagnoses; lack of previous mental

health treatment; and availability of firearms in the home (firearms were the method of suicide use in 70 percent of victims whose homes contained firearms). The authors believe this is the first report showing "that the availability of firearms is much greater in the homes of suicide completers than in those of a comparable group of at-risk youth," the authors say. This adds to the evidence that the rate of suicide by firearms is proportional to firearms availability. "Therefore, clinicians who work with suicidal adolescents should strongly advocate the removal of firearms from the home environment," they say.

MULTIPLE SCLEROSIS RISK FACTORS?

Certain occupational and leisure time exposures may be risk factors for multiple sclerosis, a Swedish study in June's *Archives of Neurology* suggests. The study by Ulf Flodin, MD, of the University Hospital, Linköping, Sweden, and colleagues examined potential MS risk factors in 83 patients and 467 other, randomized subjects. According to the authors' analysis, occupational exposure to solvents, especially in combination with welding, appeared to be associated with an excess risk for MS in males. Among females, the authors found a higher MS risk association with leisure time exposure to dogs and caged birds. A possible link between MS and animal contact has been debated for years, the authors note, with proponents of the theory suggesting the disease may be caused by a virus transmitted from dogs or cats to humans, but this theory remains controversial.

STUDY: BENEFIT OF CHEMOTHERAPY FOR COLORECTAL CANCER IS LIKELY SMALL

Most adjuvant therapies do not appear to provide any additional benefit over surgery in treating cancer of the colon and rectum, says a study in *JAMA*.

Except for chemotherapy using the anti-cancer drug fluorouracil, the study found no statistically significant benefit from any other chemotherapy or radiotherapy. These findings are based on a review of all randomized control trials of adjuvant therapy for colorectal cancer, published in English up to December 1986, say the authors, Marc Buyse, MSc, MBA, now of the European Organization for Research and Treatment of Cancer, Brussels, Belgium, and colleagues.

Because "most published trials are individually too small to rule out modest yet clinically worthwhile treatment benefits," the authors combined the results from similar trials to detect smaller beneficial effects. These trials "have an average size of about 400 patients, which is adequate to identify a major effect of treatment but grossly insufficient to detect small, yet medically worthwhile treatment benefits," the authors report. Assuming a median survival of five years after surgical treatment of colorectal cancer, "a one-year improvement would have an 80 percent chance of being detected by

observing about 1,000 deaths, a number far larger than in any of the published trials. Thus, only a combination of *all* available trials provides a reasonable chance of detecting the small benefits that can be expected from adjuvant therapy in terms of patients survival."

The authors found seventeen trials (totaling 6,791 patients, 3,348 deaths) that compared groups receiving adjuvant chemotherapy for colorectal cancer with control groups treated only with surgical removal of tumors, and eight trials (totaling 3,062 patients, 1,704 deaths) were found that compared radiotherapy groups with control groups for rectal cancer, the report says.

Their analysis shows that radiotherapy had no statistically significant effect on mortality—the odds of five-year survival were about 1.5 percent higher in patients receiving radiotherapy compared to patients in the control group.

They also found no statistically significant, overall benefit from chemotherapy. The trials, however, employed too broad a range of different chemotherapy regimens to be relevant, the authors say. When they examined trials of fluorouracil or fluorouracil-containing regimens (4,700 patients, 2,447 deaths), they found the five-year survival rate among treated patients was between 2.3 and 5.7 percent higher than the rate among control patients—though these differences were still not statistically significant. Looking only at data from trials in which fluorouracil therapy was administered for at least one year, however, they found a statistically significant, 3.4 percent higher five-year survival rate.

"Our meta-analysis provides only moderate evidence that adjuvant chemotherapy may provide an overall survival benefit but strong evidence that such benefit, if it indeed exists, would likely be small," the authors say. However, in this disease, small benefits, if real, would be far from negligible: "A five percent improvement in the five-year survival rate would correspond to an increase of about ten months in median survival... Prolonging survival by ten months in a disease that affects 140,000 persons annually in the United States and kills half of them within five years would be a major public health achievement and not a small benefit unworthy of further investigation." The authors conclude that "future trials of adjuvant therapy of colorectal cancer should be large (several thousands of patients) to detect the small treatment effects that can realistically be expected using presently known therapies."

In an accompanying editorial, Bernard Levin, MD, of the University of Texas M.D. Anderson Cancer Center, Houston, and Michael J. O'Connell, MD, of the Mayo Clinic, Rochester, Minn., say that the study's results provide little justification for the use of chemotherapy in colonic cancer "in view of the small magnitude of the putative benefits and the possibility that these results could be wiped out by failure to include any negative unpublished trials in the meta-analysis... What is needed now is the enthusiastic participation of physicians nationwide in cooperative efforts to enroll their patients in large, well-designed studies using new methods of treatment that offer even more hope," they conclude.

JAMA June 14, 1988

MARROW PROBLEMS ASSOCIATED WITH PSORIASIS DRUG REPORTED

Low-dose oral methotrexate is an accepted and effective treatment for severe psoriasis and rheumatoid arthritis. But a report in JAMA describes two psoriasis patients who suffered severe bone marrow toxicity apparently due to methotrexate use. Both patients survived but required lengthy hospitalization, says the report by Jerome L. Shupack, MD, and Guy F. Webster, MD, PhD, of the New York University Medical Center, New York City. The authors note a 1985 report in which six patients suffered similar problems apparently due to methotrexate treatment for arthritis; two died. Commenting editorially, Elizabeth A. Abel, MD, of the Stanford University School of Medicine, Stanford, Calif., and Eugene M. Farber, MD, of the Psoriasis Research Institute, Palo Alto, Calif., urge "complete patient evaluation prior to methotrexate therapy, awareness of potential drug interactions, and continued monitoring according to established guidelines."

JAMA June 24, 1988

BREAST CANCER AFTER AUGMENTATION SURGERY

Breast augmentation surgery with silicone gel implants, a procedure that has been performed on more than 1 million American women, may cloud mammography's ability to spot early signs of breast cancer, possibly delaying diagnosis, a report in June's *Archives of Surgery* says. Melvin J. Silverstein, MD, of The Breast Center and Valley Hospital Medical Center, Van Nuys, Calif., and colleagues studied 753 patients treated for breast cancer over a 66-month period; 20 of these had undergone implant surgery. None of the implant patients' cancers was spotted through mammography, the authors say. In addition, they say, implant patients presented with more advanced disease and had a higher percentage of invasive lesions and positive axillary (lymph) nodes, "resulting in a worsened prognosis." Women considering implants should not only be informed of its potential cosmetic risks and complications but should be told that "if breast cancer is destined to develop, it is possible that its diagnosis may be delayed when compared with state of the art mammographic diagnosis available in non-augmented patients," say the authors. Commenting editorially, LaSalle D. Leffall, Jr., MD, of Washington, DC, says that with the popularity of implants, physicians should be aware of the authors' findings and "notify patients of this potential occurrence." Proper placement of the implant, may reduce the clouding of mammographic detail, he says.

FATAL PEPPER ASPIRATION

A report in June's *American Journal of Disease of Children, AJDC*, describes eight cases—seven of them child abuse/homicides, one accidental—in which children died of pepper aspiration. Five of these cases had not been described previously, say the study's authors, Stephen D. Cohle, MD, of the Blodgett Memorial Medical Center, Grand Rapids, Mich., and colleagues. The reports come from a number of states (Ohio, Michigan, Massachusetts, Virginia, Missouri, Texas, Pennsylvania and New Jersey), and involved children ranging in age from 5 months to 10 years. The homicides, which the children were forced to ingest pepper by their mothers or others, "(shared) many of the features of more conventional child abuse: in each instance . . . the child was being punished, four of the seven assailants initially gave incorrect histories, and four children were chronically abused." Only one case of fatal pepper aspiration was published in the scientific literature prior to 1986, the authors say. "The facts that each death occurred in a different state and that five of the seven homicides occurred within the two years preceding the preparation of this report suggest that this form of child abuse is not confined to any single part of the country and may be increasing in frequency," the researchers conclude.

WRESTLERS' REPEATED WEIGHT LOSS MAY LOWER THEIR METABOLIC RATE

Wrestlers who repeatedly diet to "cut weight" before competition may be lowering their metabolic rate, making future weight control more difficult, says a study in JAMA.

The study compared the resting metabolic rates of high school wrestlers, who had a history of repeated cycles of weight loss and regain, with wrestlers who rarely if ever restricted food intake to cut weight. Weight losing and regaining "cyclers" were found to have a 14 percent lower daily energy expenditure than comparable non-cyclers, report the authors, Suzanne Nelson Steen, MS, RD, of the University of Pennsylvania School of Medicine, Philadelphia, and colleagues.

To gain the advantage of competing against smaller opponents, wrestlers frequently struggle to shed enough pounds before a match to qualify for a lower-weight category. Even though the American College of Sports Medicine and the American Medical Association have issued position statements that strongly discourage food and fluid deprivation used by wrestlers, the practice is still widespread, says the report.

One study of college wrestlers showed 81 percent reduced food intake, 21 percent fasted, and 58 percent used fluid restriction to cut weight. "Wrestlers typically use fluid-restriction, artificial methods of dehydration (e.g. diuretics, rubber sweatsuit or sauna), and food restriction to lose weight," the authors say. "It is

common for wrestlers to fast or severely restrict intake before a meet and then to consume large amounts of food afterward, creating a cycle of fasting-overeating-fasting."

The practice of "weight cutting" may have undesirable health consequences, the authors say. "Studies have shown adverse effects on body composition, nutrient intake, renal function and electrolyte balance, thermal regulation, testosterone levels, and strength." Since animal and human studies suggest that the body adapts to repeated dieting and weight loss by lowering energy requirements, the authors decided to measure the metabolic consequences of wrestlers' weight loss practices.

Fourteen wrestlers who were "cyclers" were matched with 13 non-cyclers. "Cyclers and non-cyclers did not differ in age, weight, height, surface area, lean body mass, or percent body fat," the authors report. The resting metabolism of all subjects was calculated from measurements of respiratory gas exchange rates while subjects were at rest. The measurements showed that cyclers have a 14 percent lower metabolic rate than do non-cyclers.

The authors point out that, though strongly suggestive, their findings do not prove cause and effect. "Wrestlers with low energy requirements might have difficulty controlling their weight, thus making weight cutting necessary to achieve a competitive weight... Prospective studies will be needed to determine whether weight cycling actually produces a decline in metabolic rate."

"Weight restriction and fluctuation may alter health status, either directly through the influence of weight or indirectly through the effects of diet and exercise behaviors used to accomplish these changes," the authors conclude. "If a wrestler's metabolic rate decreases, subsequent dieting will become increasingly frustrating, both during the wrestling season and later in life."

JAMA July 1, 1988

STUDY FINDS DRAMATIC INCREASE IN RARE SKIN CANCER

The incidence of mycosis fungoides, a slowly progressive, usually fatal lymphoma that effects the skin, has dramatically increased in the United States between 1969 and 1984, says a report in *JAMA*.

Though mycosis fungoides is still one of the rarer forms of cancer, the study documents a 3.2-fold increase in the incidence of the disease over the 14-year period ending in 1984, say the authors Martin A. Weinstock, MD, PhD, of the Harvard Medical School, Boston, and John W. Horm, MSc, of the National Cancer Institute, Bethesda, Md.

Data for their study came primarily from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. "The SEER program was begun in 1973 for the purpose of routinely monitoring cancer incidences and survival in a large portion of the U.S. population," the authors report. "Data was collected from nine geographically defined areas of the United States: the metropolitan areas of San Francisco-Oakland, Detroit, Seattle-Puget Sound, and

Atlanta as well as the entire states of Connecticut, Utah, Iowa, New Mexico, and Hawaii."

Only 721 new cases of mycosis fungoides were reported from 1973 through 1984, the last year SEER data was available for their study. However, the incidence had risen sharply over this 12-year period for reasons unknown, the authors report. In 1973, mycosis fungoides cases made up only 1.6 percent of all cases of lymphomas; in 1984, they made up 2.8 percent. Based on these data and on data from the Third National Cancer Survey, the authors estimate the annual incidence of mycosis fungoides in 1969-1971 was about one case per 769,000 persons. The incidence climbed fairly steadily over this 14-year period to approximately one case per 238,000 persons in 1984, a 3.2-fold increase.

This same dramatic rise in incidence rate is observed in each stratum of age, sex, race, and in most SEER program registries over the 12-year period, the authors report. "Blacks were twice as likely to be afflicted as whites, and the incidence among men was more than twice the incidence among women. The geographic variation in incidence was associated with several demographic variables, including population density, family income, and concentration of physicians." Although the later association suggests that earlier diagnosis may have led to the increase in reported incidence, the authors say that "analysis of mortality among these patients revealed no evidence of detection bias."

The cause of mycosis fungoides is unknown and there is yet no cure. The cancer progresses slowly and, because it occurs much more often among the elderly, about one third of patients die of other causes associated with aging, rather than from the lymphoma. "These patterns of incidence (from their study) may be used to evaluate proposed causes in an effort to understand and, ultimately to prevent this disorder," the authors conclude.

JAMA July 1, 1988

INCREASING AUTOLOGOUS BLOOD SUPPLIES

A study in *JAMA* suggests that the use of a genetically engineered human hormone may enable more patients to donate enough of their own blood prior to elective surgery to avoid the risk of using blood from other donors. The study of autologous donors showed that successive donations caused anemia in most of the donors, and many weren't able to supply enough blood to meet their surgical needs. The authors, Thomas S. Kickler, MD and Jerry L. Spivak, MD, of The Johns Hopkins University School of Medicine, Baltimore, report that the anemia was insufficient to adequately increase their levels of erythropoietin, the hormone that stimulates red-blood cell production. Therefore, the use of recently available recombinant human erythropoietin may help autologous donors supply enough of their own blood for later transfusions, they write. "This practice has the potential for not only reducing the risks of transfusion but also increasing the overall blood supply."

JAMA July 1, 1988

INSTRUCCIONES PARA LOS AUTORES*

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

Se urge a los autores se esfuercen en perseguir claridad, brevedad, e ir a lo pertinente en sus manuscritos no importa el tema o formato del manuscrito.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y la del impresor, se requiere de los autores que sigan las siguientes instrucciones:

Manuscrito

El manuscrito completo, incluyendo las leyendas y referencias deberán estar escritos en maquina a doble espacio; por un solo lado de cada página, en TRIPLICADO y con amplio margen. En página separada deberá incluirse lo siguiente: título, nombre del autor(es) y su grado (ej: MD, FACP), ciudad donde se hizo el trabajo, el hospital o institución académica, patrocinadores del estudio, y si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

El manuscrito debe comenzar con una breve introducción en la cual se especifique el propósito del mismo. Las secciones principales (como por ejemplo: materiales y métodos) deben identificarse con un encabezamiento en letras mayúsculas.

Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: Introducción, Materiales y Métodos, Resultados, Discusión, Resumen (en español e inglés), Reconocimiento y Referencias.

Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: Introducción, Materiales y Métodos si es aplicable, Observaciones del Caso, Discusión, Resumen (en español e inglés), Reconocimientos y Referencias.

Nomenclatura

Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea. Se usará con preferencia el sistema métrico de pesos y medidas.

Tablas

Las tablas deben aparecer en hojas separadas. Estas deben incluir el título, y el número de la tabla debe estar en romano. Los símbolos de unidades deben limitarse al encabezamiento de las columnas. Se deben omitir líneas verticales en la tabla. Se usará en las tablas el mismo idioma en el cual está escrito el artículo. Deben limitarse las tablas a solo aquellas que contribuyan al mejor entendimiento del manuscrito.

Ilustraciones

Las fotografías y microfotografías se someterán como copias en papel de lustre, sin montar o en transparencias. En el reverso de la figura debe aparecer el número de la figura (arábigo) y el autor. Debe indicarse la parte superior de la ilustración.

Resumen

Un abstracto no mayor de 150 palabras debe acompañar los manuscritos. Debe incluir los puntos principales que ilustren la substancia del artículo y la exposición del problema, métodos, resultados y conclusiones.

Referencias

Las referencias deben ser numeradas sucesivamente de acuerdo a su aparición en el texto. Los números deben aparecer en paréntesis al nivel de la línea u oración. Al final de cada artículo las referencias deben aparecer en el orden numérico en que se citan en el texto. Deben utilizarse solamente las abreviaturas para títulos de revistas científicas según indicadas en el "Cumulative Index Medicus" que publica la Asociación Médica Americana. Las referencias deben seguir el patrón que se describe a continuación.

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Si hay más de 7 autores, incluir los primeros 3 y añadir et al.
2. Para citación de libros donde el autor(es) del capítulo citado es a su vez el (los) editor(es): Apellido(s) e iniciales del autor(es), título del libro, número de edición, ciudad, casa editora, año y página. Por ejemplo:
Keith JD, Rowe RD, Vlad P: Heart disease in infancy and childhood, 3d. Ed., New York, MacMillan, 1978: 789
3. Para citación de libros donde el editor(es) no es el autor(es) del capítulo citado se añade el autor(es) del capítulo y el título del mismo. Por ejemplo:
Olley PM: Cardiac arrhythmias. In: Keith JD, Rowe RD, Vlad P. Eds. Heart disease in infancy and childhood, 3d Ed., New York, MacMillan, 1978: 275-301

Cartas al Editor

Se publicarán a discreción de la Junta Editora. Deben estar escritas en maquina a doble espacio, no deben ser mayores de 500 palabras, ni incluir más de cinco referencias.

*Estas "Instrucciones para los Autores" son de acuerdo a las normas establecidas por el Comité Internacional de Editores de Revistas Médicas en sus "Requisitos Uniformes para Manuscritos Sometidos a Revistas Bio-Médicas".

INSTRUCTIONS TO AUTHORS*

The Bulletin will accept for publication contributions relating to the various areas of medicine, surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

All authors are urged to seek clarity, brevity, and pertinence in the manuscripts regardless of subject or format.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

Manuscripts

The entire manuscript, including legends and references should be typewritten double spaced in TRIPLICATE with ample margins. A separate title page should include the following: title, authors and their degrees (e.g. MD, FACP), city where the work was done, hospital or academic institutions, acknowledgement of financial sponsors, and if the paper has been presented at a meeting the place and date should be given.

The manuscripts should start with a brief introductory paragraph or paragraphs which should state its purpose. The main sections (for example, Materials and Methods) should be identified by headings in capital letters.

Articles reporting the results of clinical studies or laboratory investigation should be organized under the following headings: Introduction, Material and Methods, Results if indicated, Discussion, Summary in English and Spanish, Acknowledgments if any, and References.

Nomenclature

Generic names of drugs should be used; trade names may also be given in parenthesis, if desired. Metric units of measurement should be used preferentially.

Tables

These should be typed on separate sheets with the title and table number (Roman) centered. Symbol for units should be confined to the column headings. Vertical lines should be omitted. The language used in the tables must be the same as that of the article. Include only those tables which will enhance the understanding of the article. They should supplement, not duplicate the text.

Figures

Photographs and photomicrographs should be submitted as glossy prints, (unmounted) or slides. They should be labeled in the back with the name of the authors and figure number (Arabic) and the top should be indicated. Legends to the figures should be typed on a separate sheet.

Summary

An abstract not longer than 150 words should accompany all articles. It must include the main points that present the core of the article and the exposition of the problem, method, results, and conclusions.

References

These should be numbered serially as they appear in the text. The number should be enclosed in parenthesis on the line or writing and not as superscript numbers. At the end of the article references should be listed in the numerical order in which they are first cited in the text. The titles of journals should be abbreviated according to the style used in the "Cumulative Index Medicus" published by the American Medical Association. The correct forms of references are as given below:

1. For periodicals: Surname and initials of author(s), title of article, name of journal, year, volume, pages. For example:
Villavicencio R: Soplos inocentes en pediatría. Bol Asoc Méd P R 1981; 73: 479-87
If there are more than 7 authors list only 3 and add et al.
2. For books when the authors of the cited chapter is at the same time the editor: Surname and initials of author(s), title, edition, city, publishing house, year and page. For example:
Keith JD, Rowe RD, Vlad P: Heart disease in infancy and childhood, 3d Ed., New York, MacMillan, 1978: 789
3. For chapter in book when the author of the chapter is not one of the editors:
Olley PM: Cardiac arrhythmias. In: Keith JD, Rowe RD, Vlad P. Eds. Heart disease in infancy and childhood, 3d Ed. New York, MacMillan, 1978: 275-301

Letters to the Editor

Will be published at the discretion of the Editorial Board. They should be typewritten double-spaced, should not exceed 500 words nor more than five references.

*The above "Instructions to Authors" are according to the format required by the International Committee of Medical Journal Editors in its "Uniform Requirements for Manuscripts Submitted to Biomedical Journals".

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References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Feighner VP, et al: *Psychopharmacology* 61:217-225, Mar 22, 1979.

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Warnings: Use with caution in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur when used with anticholinergics. Closely supervise cardiovascular patients. Arrhythmias, sinus tachycardia, prolongation of conduction time, myocardial infarction and stroke reported with tricyclic antidepressants, especially in high doses. Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

Adverse reactions not reported with Limbitrol but reported with one or both components or closely related drugs: **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, increased or decreased libido. **Neurologic:** Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns. **Anticholinergic:** Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract. **Allergic:** Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus. **Hematologic:** Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue. **Endocrine:** Testicular swelling, gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion. **Other:** Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

Overdosage: Immediately hospitalize patient. Treat symptomatically and supportively. I.V. administration of 1 to 3 mg physostigmine salicylate may reverse symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

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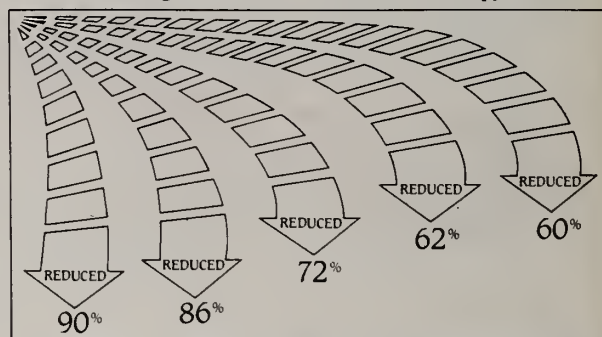
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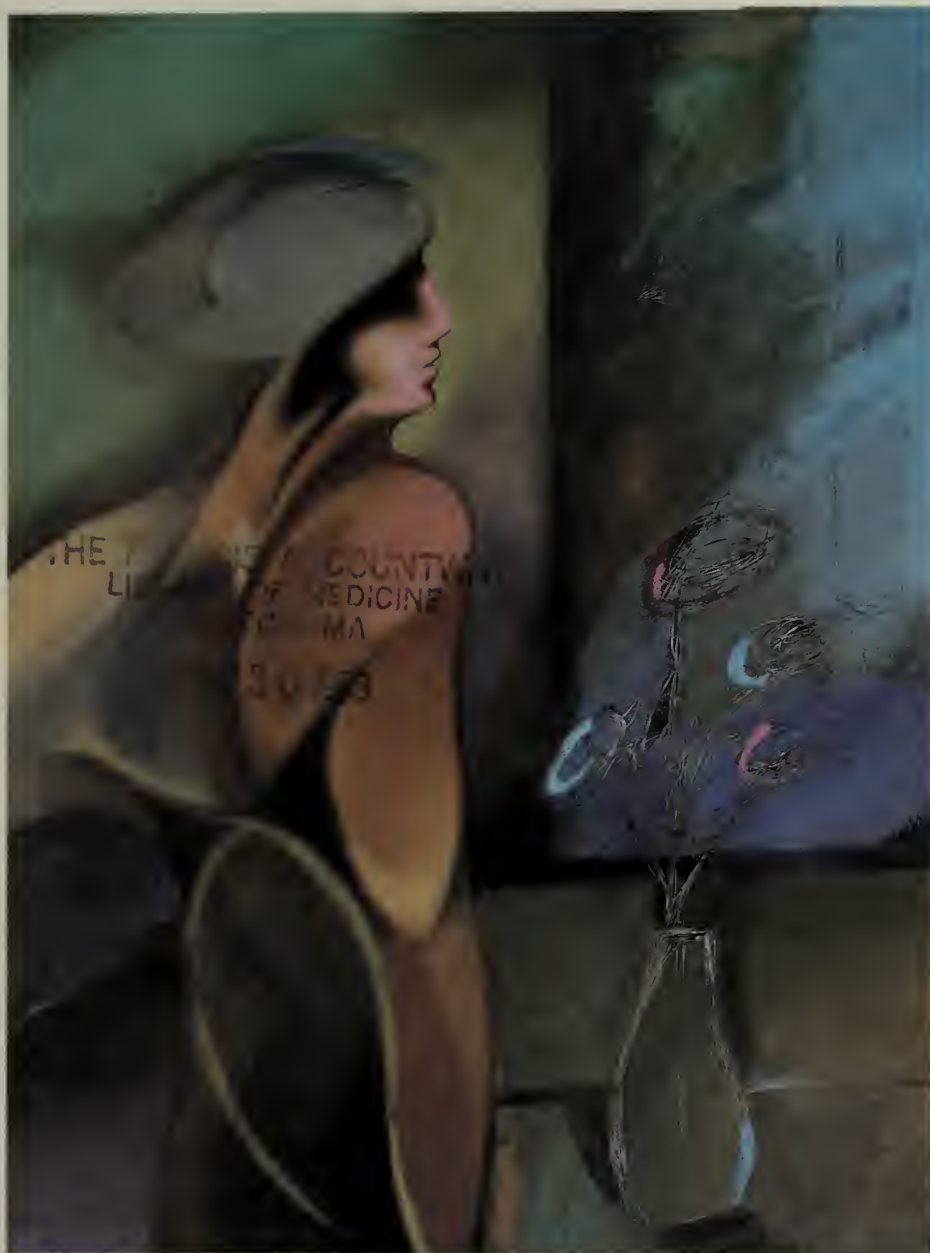
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VOL. 80 / NUM. 9

SEPTIEMBRE 1988



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VOL.80 - NUM. 9

SEPTIEMBRE 1988

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Publicación mensual, \$40.00 anuales. El Boletín se distribuye a todos los miembros de la Asociación Médica de Puerto Rico como parte de su cuota anual.

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Boletín de la Asociación Médica de Puerto Rico is published monthly for \$40.00 per year by Asociación Médica de Puerto Rico. 1305 Fernández Juncos Ave. P.O. Box 9387, Santurce, P.R. 00908.

"POSTMASTER" Send address changes to Boletín Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, Santurce, P.R. 00908.

Second Class postage paid at San Juan, P.R.

USPS-060000

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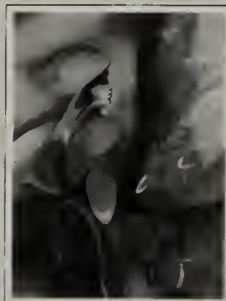


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VOL. 80/NUM. 9 SEPTIEMBRE 1988

NUESTRA PORTADA

Luz de Mañana, por Juan Ramón Velázquez. El artista hace su entrada al ambiente cultural puertorriqueño a principios de los años setenta con sus dibujos de dramático impacto y temas intensos. Su trabajo se destaca rápidamente y comienza a exhibir en varias galerías y museos de la isla y muy pronto proyecta sus trabajos hacia el exterior.

Sus dibujos van evolucionando tanto en la técnica como en la temática por espacio de varios años durante los cuales su trabajo es ya muy apreciado por los más estrictos conocedores del arte de nuestro país.

A principio de la década actual es ya un reconocido dibujante, tanto en Puerto Rico como en algunos países en Latinoamérica. Es para esta época que el artista empieza a incursionar en la pintura. En 1982 gana el Premio Unico de la muestra de pintura de la Unesco con uno de sus primeros trabajos en acrílico.

A partir de entonces Velázquez se dedica con más intensidad a pintar sin nunca abandonar su trabajo en el dibujo. Hoy en día Juan Ramón Velázquez es uno de los más reconocidos artistas de su generación, caracterizándose su trabajo por una depurada técnica, original y singular estilo tanto de dibujante como de pintor, en el cual sus enigmáticas figuras dominan los espacios en que habitan.

En su trabajo ha incorporado nuevos conceptos plásticos como es el romper y coser los papeles y los lienzos creando singulares "collages" de impactantes efectos.

La obra en la portada titulada "**Luz de Mañana**" es una pintura reciente del año 1987 y representativa del trabajo de Juan Ramón Velázquez. Una obra similar será sorteada entre los miembros de la Sección de Oftalmología durante nuestra convención el próximo noviembre. La Junta Editora agradece al Dr. José Luis Fossas, Presidente de la Sección de Oftalmología su colaboración para poder publicar esta obra en la portada de nuestro Boletín.

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DERMATOLOGY DIAGNOSIS

David G. Latoni, MD
Jorge L. Sánchez, MD

A 31-year-old woman without history of any systemic illness was evaluated in our Clinic with a six months history of an asymptomatic, papulo-nodular eruption. The patient stated that this eruption started on her face and followed in a short period of time by new lesions on her arms, legs, buttocks and shoulders. She pointed out that some of these lesions progressively increased in size with the formation of large dark nodules. The patient denied weight loss, fever, chills, or symptoms referable to the respiratory, cardiac or visual systems. The patient also denied a past history of tuberculosis, syphilis or any systemic infectious disease. The family history was unremarkable.

The physical examination revealed a well-nourished young female with normal vital signs and in no acute distress. There were multiple hyperpigmented, infiltrated, firm, papules and nodules on her face, arms, thighs, buttocks, and shoulders. The facial lesions tended to have a predilection for the periorificial areas of skin. The rest of the physical examination was within normal limits.

Chest X-Rays disclosed bilateral hilar adenopathies and an SMA-20 revealed slightly elevated calcium levels. Angiotensin-converting enzyme levels, serum protein electrophoresis, electrocardiogram, complete blood count, urinalysis and VDRL were within normal limits. Skin cultures and tuberculin test were negative.



WHAT IS YOUR DIAGNOSIS?

- A- Secondary lues
- B- Tuberculosis cutis
- C- Sporotrichosis
- D- Sarcoidosis
- E- Tuberculoid leprosy

Diagnosis: Sarcoidosis

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology, most commonly affecting young adults and presenting more frequently with bilateral hilar lymphadenopathy, pulmonary infiltrates and skin or eye lesions. The diagnosis is established most accurately when clinical and radiographic findings are supported by histological evidence of non-caseating epithelioid cells granulomas. Even though the etiology of sarcoidosis remains obscure, various infectious agents have been implicated, including mycobacteriae, fungi, and viruses. Figures for local prevalence are highly variable but have been reported to be as high as 200 per 100,000 population in certain communities, and appears to be more prevalent in developed countries. Adults under the age of 40 years, especially women and blacks, are more commonly affected, have more atypical cutaneous involvement and present a more complicated clinical course. No consistent mode of inheritance has been observed, although an increased frequency of HLA-B8 has been detected among these patients.

Cutaneous lesions are observed in approximately 20% to 35% of patients with systemic sarcoidosis. It has been estimated that dermatologic manifestations of sarcoidosis first cause patients to seek medical attention in approximately 10% of cases, and at least 50% of patients who are initially evaluated for dermatologic complaints have either pulmonary disease at the time of presentation or subsequently develop pulmonary sarcoidosis.

Cutaneous manifestations of sarcoidosis can be divided into specific and non-specific lesions. Specific lesions are those that on biopsy reveal non-caseating granulomas; these are seen in approximately 10% to 35% of patients and are usually associated with an unfavorable course. Non-specific lesions are those which on biopsy fail to reveal granuloma formation but are associated with sarcoidal involvement in other systems.

Erythema nodosum usually manifests as subcutaneous, erythematous, warm, tender and symmetrical nodules most commonly on the shins, but are also frequently seen on the calves, knees, buttocks, and less commonly on the arms. The onset is abrupt and may be accompanied by a flu-like syndrome with fever, fatigue, arthralgias, uveitis, elevated sedimentation rate and bilateral hilar adenopathies, comprising the so called Löfgren's syndrome. Nonspecific therapy is indicated, since usually the disease, including its pulmonary manifestations tend to spontaneously involute in approximately 80% of patients within six months. Young individuals, with a mean age of 30 years in some studies, appear prone to be affected. More than 90% of patients with erythema nodosum and approximately 70% of patients with other skin manifestations also present pulmonary sarcoidosis.

Lupus pernio represents a specific cutaneous manifestation of sarcoidosis. It presents as a chronic, persistent, violaceous, nodular or plaque-like eruption with a predilection for the nose, cheeks, and ears. There may be nodules on the eyelids and ears with associated plaques on the arms, buttocks, and thighs. It has an insidious onset and rarely resolves. Lupus pernio most commonly affects women on their fourth or fifth decades. Lupus

pernio has a closer affinity with sarcoidosis of the upper respiratory tract, and is commonly associated with fibrotic changes in the lungs, bone cysts, and eye and lymph node involvement. The lesions of lupus pernio often result in considerable deformity, with fibrosis and scarring. Corticosteroid therapy and methotrexate are effective treatments for lupus pernio, but relapses following withdrawal of treatment are common.

Papules, plaques and nodular lesions such as the ones presented in this case also have an insidious onset and are most commonly observed on the face, extremities, buttocks and shoulders. They are of a firm consistency and diffusely infiltrated. When telangiectasis is a prominent finding the term "angiolupoid" is used. These lesions may be annular or serpiginous. Histologically they reveal non-caseating granulomas involving the full thickness of the dermis with sparing of the nerves. An association between these lesions and ophthalmologic disease is commonly observed.

A transient maculo-papular or vesicular eruption with histopathologic changes of sarcoid may be observed at the onset of the disease. It tends to be symmetric and most commonly involves the face, trunk, arms, dorsum of limbs and nuchal area. This eruption tends to be associated with uveitis, parotid gland enlargement, early intrathoracic involvement or acute lymphadenopathy. It usually resolves within a month with post inflammatory hyper or hypopigmentary changes, but it may recur with an exacerbation of iridocyclitis.

Scar tissue may frequently contain sarcoidal infiltrates. They include scars on the abdomen, neck, cutaneous venesection sites and tuberculin skin test sites among others. Clinically these previously atrophic scars suddenly become purple and livid thus resembling keloids. Biopsy reveals active sarcoid tissue within these scars.

Other occasionally observed cutaneous manifestations of sarcoidosis include the ichthyosiform and erythrodermic forms which present as erythematous, scaling, infiltrating lesions, often associated with lymphadenopathy, and a tendency to resolve spontaneously. Hypopigmented lesions consisting of macules, papules or plaques surrounded by areas of hyperpigmentation, and presenting a localized or generalized distribution are rarely observed. Subcutaneous sarcoid presents as persistent movable and painful nodules. Other less commonly observed manifestations include ulcerative, multilobular, psoriasiform, lupus-like lesions and scarring alopecia.

Systemic manifestations of sarcoidosis include some combination of intrathoracic adenopathy and pulmonary parenchymal fibrosis, which can be classified according to the stage of involvement. Stage 1 disease consists of bilateral hilar adenopathy without parenchymal involvement. Stage 2 disease is characterized by the presence of bilateral hilar adenopathy and pulmonary fibrosis. Stage 3 describes patients with extensive interstitial fibrosis without hilar adenopathy. About 70% to 80% of patients with stage 1 disease will resolve spontaneously. Erythema nodosum is more commonly associated with stage 1 disease, while stage 2 and 3 are more commonly associated with chronic pulmonary sarcoidosis. Pulmonary fibrosis has been observed to correlate with the presence of chronic plaque-like lesions

as well as lupus pernio.

Ocular involvement is the second most common manifestation of sarcoidosis and is seen in 25% to 50% of patients with systemic disease, uveitis and chorioretinitis being the most common manifestations. Also conjunctival granulomas can be detected in up to one third of patients.

Neurologic sarcoidosis is present in 5% to 15% of patients, and the most common site affected within the central nervous system is the facial nerve. The pituitary gland and hypothalamus are involved less often.

Lymphadenopathy with involvement of peripheral nodes occurs in about 75% of patients. Other less commonly observed involved organs in sarcoidosis include the spleen, liver, heart, muscle, bone, bone marrow, and kidney.

The most typical biopsy finding is that of a non-caseating granuloma composed of epithelioid cells and Langhan's giant cells, surrounded by lymphocytes, macrophages and fibroblasts. The enzymes secreted by the granulomata include angiotensin-converting enzyme, lysozyme, glucuronidase, collagenase, and elastase. Although the presence of an elevated level of angiotensin-converting enzyme has proved a valuable indicator of disease activity, the presence of elevated levels of this enzyme in other conditions makes its role as a diagnostic aid questionable.

There is immunologic evidence of depression of delayed hypersensitivity with a relative increase of T-suppressor cells in the peripheral blood, along with an increased number and activity of T-helper cells in the lung and bronchoalveolar fluid. Also, there is evidence of lympho-proliferation with increased activity of B-cells and in-vitro overproduction of immunoglobulins, which may account for the polyclonal hyperglobulinemia and the presence of circulating immune complexes.

Laboratory findings include hypercalcemia, hypercalciuria, hydroxyprolinuria, elevated immunoglobulins IgA, IgG and IgM, elevated serum B-2 microglobulins, elevated sed rate, and increased T helper to T suppressor ratio. Serum angiotensin converting enzyme (ACE) is said to be elevated in 60% of patients with sarcoidosis and 10% of patients with other diseases. ACE levels are most beneficial as a monitor of progress. In a study by Callen et. al. they found that in those patients with sarcoidosis localized to the skin, ACE levels may be elevated and do not necessarily reflect the presence of systemic disease. Serum and urinary lysozyme levels may be elevated but also are of limited value.

For diagnostic purposes the evaluation of a patient with sarcoidosis should include a physical examination, chest x-rays, ophthalmologic evaluation, electrophoresis and a Kveim test. The Kveim-Siltzbach test is said to be positive in about 80% of patients but it has been reported to be negative in the absence of hilar adenopathy, thus making it of little value in extrathoracic disease. Histopathologic confirmation is necessary in most cases, and it is most commonly obtained from the skin, lung or lymph nodes. In selected cases with pulmonary involvement the performance of fiberoptic bronchoscopy with transbronchial lung biopsy provides a tissue source for examination.

Therapy is aimed at preventing progression, promoting regression, and alleviating symptoms of the disease.

Corticosteroids are the major form of treatment in sarcoidosis and are particularly indicated for uveitis, worsening of chest x-ray findings, persistent hypercalciuria, breathlessness, disfiguring skin lesions, myocardial involvement, neurologic involvement, hypersplenism, renal insufficiency secondary to hypercalciuria and symptomatic salivary or lacrimal gland involvement. Other forms of adjuvant therapy such as intralesional steroids for cutaneous lesions, steroid eyedrops for uveitis and non-steroidal antiinflammatory agents for erythema nodosum are indicated in certain patients. Chloroquine may have a beneficial effect on cutaneous involvement, but relapses after discontinuation are commonplace. Oxyphenbutazone has been effective in some cases of systemic disease. Methotrexate may be effective in lupus pernio and ocular involvement.

Despite the significant morbidity associated with all forms of sarcoidosis, mortality figures at present are only 3% to 6% of patients affected.

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El Comité del Programa Científico invita a enviar resúmenes de ponencias de trabajos originales para considerarse para presentación durante la sesión científica que se efectuará los días 14, 15 y 16 de octubre de 1988.



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CLINICAL STUDIES

Acquired Immunodeficiency Syndrome (AIDS) and Parasitic Diseases in Puerto Rico

George V. Hillyer, Ph.D.
Consuelo Climent, MD

Abstract: In Puerto Rico, since the first diagnosis and death due to acquired immunodeficiency syndrome (AIDS) in 1981, the numbers of cases and deaths have increased steadily to 1253 cases and 741 deaths as of May, 1988 (Update note: 1526 cases and 900 deaths as of August 2). On the mainland USA the preponderance of AIDS cases are due to homosexual or bisexual males. The cases in Puerto Rico differ from those of the mainland in that they are mostly heterosexual drug addicts. Moreover, parasitic infections are commonly seen in association with AIDS cases and deaths in Puerto Rico. Those parasitic infections most commonly seen are *Pneumocystis carinii* pneumonia, and *Toxoplasma gondii* meningoencephalitis. Others less commonly seen include infection with *Schistosoma mansoni* and *Strongyloides stercoralis*. Cases of infection with *Isospora belli* (n = 1) and *Cryptosporidium* (n = 2) have also been observed pre mortem, but were not present at autopsy. This article reviews the current status of these parasitic infections, their life cycles, and their diagnosis in relation to AIDS in Puerto Rico.

Retroviruses infect numerous vertebrate hosts and cause a wide variety of diseases including malignancies, immunodeficiencies, aplastic and hemolytic anemias, and neuropathies.¹ Until 1980, no human retroviruses were known, but now, four distinct viruses with a tropism for human T4 lymphocytes have been described as natural infections of humans. Today, these four retroviruses are designated HTLV-1, HTLV-2, HIV-1, and HIV-2. Retroviruses are characterized by possessing the enzyme reverse transcriptase (RNA directed DNA polymerase). Upon infection, this enzyme catalyses synthesis, from the virion RNA, of a DNA 'provirus' which subsequently becomes integrated into host chromosomal DNA. This can lead to latent infection in which the provirus persists and is passed to daughter cells in mitosis, or to full replication which is frequently not cytotoxic. Most retroviruses carry three genes in the order 5'-gag-pol-env-3'. Gag encodes a precursor protein that is cleaved to yield 3-4 virion core proteins, pol encodes the

reverse transcriptase, and env encodes a precursor cleaved to form the two disulphide-linked envelope proteins, at least one of which is glycosylated. Of the four major classes of human retroviruses, two are clearly linked to human disease:

1. T cell lymphotropic oncoviruses (including HTLV-1 and HTLV-2) associated with leukemia and lymphoma and possibly implicated in tropical neuropathies.
2. T cell lymphotropic lentiviruses (=human immunodeficiency viruses, including HIV-1 and HIV-2) associated with acquired immunodeficiency syndrome (AIDS, see below).

The group of retroviruses classified as the Human Immunodeficiency Viruses (HIV) are the known etiologic agents for AIDS. There are currently two types of HIV virus: HIV-1 (formerly HTLV-III or LAV-1) and HIV-2 (formerly HTLV-IV or LAV-2). HIV are transmitted primarily during sexual contact, through parenteral exposure to blood and blood products including the sharing of needles by intravenous drug users, and from mother to child during the perinatal period. AIDS is an invariably fatal disease for which there is neither effective long-term treatment nor available vaccination. Since 1981, more than 70,000 cases of AIDS have been reported from more than 127 countries. Of these, nearly 50,000 cases have been reported in the United States of which 56% were reported to have died, including over 80% of those diagnosed before 1985. During the past 12 months, 20,745 reports were received, an increase of 57% over the preceding year. Thus, HIV infection and AIDS are now major causes of morbidity and mortality in the United States.²

HIV-1 is the primary etiologic agent of AIDS. More recently, HIV-2 infection has been reported primarily in West Africa and Europe. In the USA the first reported case of AIDS due to HIV-2 infection was diagnosed in December 1987 of a West African who came to the U.S. that year. A CAT scan of the brain revealed mass lesions that biopsy showed to be caused by *T. gondii*. The patient's serum revealed a negative ELISA for antibody to HIV-1 with an indeterminate HIV-1 immunoblot. However, ELISA antibodies to HIV-2 (Genetic Systems Corp. Seattle) were repeatedly reactive and HIV-2 immunoblot revealed bands for antibodies to gag (p26),

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pol (p34), and *env* (gp 140) proteins.³ Since HIV-1 is the overwhelmingly common etiologic agent of AIDS in the U.S. and the Caribbean (HIV-2 has not been identified in the Caribbean to date), all subsequent references to HIV imply HIV-1 unless otherwise stated.

Common to all AIDS cases is the development of a profound cellular immunosuppression caused by the HIV, and which has been shown to be the primary etiologic agent of AIDS. The virus has specific tropism for T-helper/inducer (T4-positive) lymphocytes causing its selective depletion. HIV also has tropism for the brain leading to neuropsychiatric abnormalities. Besides inducing cell death, HIV can interfere with T4 cell function by various mechanisms.⁴ While the viral etiology and immunopathogenesis are common to all patients with AIDS, the epidemiology and clinical features vary in different countries, depending on cultural differences, the presence of other endemic diseases, and other unidentified risk factors. Perhaps the most striking difference noted in the epidemiology of AIDS has been the 1:1 male:female ratio observed among African patients with AIDS, compared with the 13:1 ratio initially reported among the American and European patients with AIDS, in whom male homosexual contact is a major modality of transmission of HIV.

Studies on the natural history of HIV-1 infection in homosexual men in Europe and North America have shown annual progression rates of ca. 2-5%. It is also known that in Europeans prognostic factors for disease progression include a specific loss of IgG antibodies against the HIV-1 *gag* gene and *gag* gene products (p24), while antibody to the viral envelope glycoprotein remains stable.⁵

AIDS in Puerto Rico

The diagnosis and first case of death due to AIDS in Puerto Rico was identified in 1981. Since then, the numbers of cases and the numbers of deaths have steadily increased to 1253 cases and 741 deaths (CLETS Surveillance Report, 5/12/87). [Update note: As of August 2 the numbers of cases rose to 1526 and the number of deaths to 900 - Ralph Perez, CLETS, personal communication]. Through May, 1988 98% of the adult cases of AIDS in Puerto Rico and all of the pediatric cases were hispanics. A summary of the numbers of AIDS cases and deaths due to AIDS is found in Figure 1. The overwhelming disease category reported by the PR AIDS reporting system is *Pneumocystis carinii* pneumonia. No other parasitic disease is reported.

The first comprehensive study on the pathology of AIDS in Puerto Rico was published by Climent, *et al.* who reported on the first 20 cases seen.⁶ The most common diagnosis (and only parasitic infection reported then) was *Pneumocystis carinii* pneumonia (75%). However, when the histopathology of 58 men and 6 women (n = 64) who died of AIDS in PR was studied, the following parasites were found: *Pneumocystis carinii* was overwhelmingly the one most commonly seen (38 patients, 59%), *T. gondii* (n = 13; 20%), *Schistosoma mansoni* (n = 6; 9%), and *S. stercoralis* (n = 2; 3%).⁷ In contrast to patients with AIDS who live on the mainland

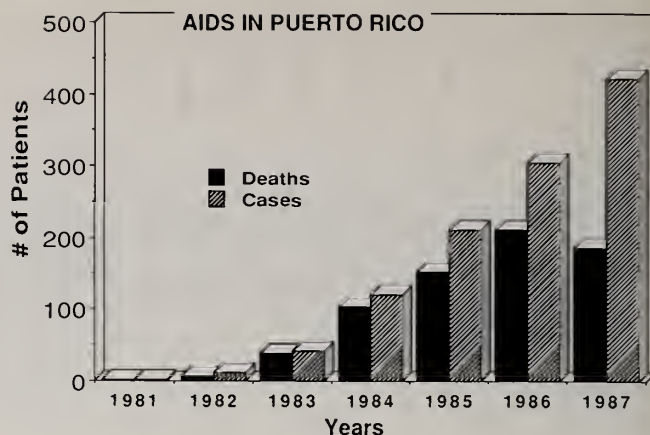


Figure 1. The number of AIDS cases and deaths in Puerto Rico from 1981 through 1987 as reported by the CLETS Surveillance Report of May 12, 1988.

An additional 137 cases and 40 deaths were reported through May 12, 1988 for a total, since 1981, of 1253 cases and 741 deaths.

USA, 70 % of the patients in PR were intravenous drug abusers and only 26% were homosexual men. Moreover, some Puerto Rican patients with AIDS and infection with *T. gondii* in brain also had myocarditis due to *T. gondii*. Thus, in Puerto Rican patients, myocarditis due to an infectious pathogen (*T. gondii*) should be suspected in all AIDS patients with toxoplasmosis.⁸

To date, the Puerto Rican AIDS patient population consists primarily of drug addicts, with homosexuals who are not drug abusers comprising less 33% of the patient population, drug addicted heterosexuals 51% and drug addicted homosexuals or bisexuals 14%. AIDS pathology registry is in place in collaboration with the Armed Forces Institute of Pathology in Washington, D.C. An analysis of the data gathered though it reveals that neither the opportunistic pathogens nor the opportunistic neoplasms affecting our population are the same in type or distribution as those found in the mainland. Additionally, in Puerto Rico AIDS is not attended by the high incidence of Kaposi's sarcoma as the initial opportunistic phenomenon. A third important difference is that in many of our drug-addicted AIDS patients follow an extremely virulent course, with death occurring in a span of 4-5 months after the onset of symptoms. We hypothesize that the disimmunity state our patients suffer is probably more profound than the one observed elsewhere but this needs to be studied in more detail. Parasitic infections are more common in these patients than their cohorts on the mainland and these infections may also influence the natural history of HIV infection. Another reason behind the galloping version of the disease seen in drug addicts in Puerto Rico may lie in the problem of reticuloendothelial system (RES) blockade. Many illicit intravenous drugs are diluted with particulate matter (such as talc). Intravenous particulate matter is phagocytized, and an RES blockade ensues that lasts about 24 to 48 hours. During this period the RES system is rendered incapable of dealing with circulating pathogens, pathogens which may in fact enter the bloodstream in conjunction with the drug. The combina-

tion of a blocked RES and a suppressed immune system abrogates all chances of defense. As a result, the testing of nationally developed protocols requires that we perform numerous sequential measurements of the status of the immune system to take prompt and corrective action. In addition to the above, some faculty members are engaged in projects aimed at developing immunomodulators that show promise in strengthening protective immunity in these patients.⁹ Preliminary results in animals have demonstrated that a polyantigenic vaccine comprised of antigens from ubiquitous microorganisms has this effect.

Serodiagnosis of HIV

Licensed test kits currently available in the United States for HIV antibody testing comprise 7 enzyme immunoassays (EIA) and one Western blot (WB). All of these tests use HIV antigens derived from disruption of whole virus cultured in human-derived cell lines. Criteria for interpretation of a reactive anti-HIV EIA test are based on data from clinical studies performed under the auspices of each manufacturer.¹⁰ The WB technique has been recommended as the procedure of choice for the confirmation of the presence of HIV antibodies in a sample of serum or plasma. In this procedure, individual viral proteins are separated by gel electrophoresis from contaminating cellular proteins, and from one another, into discrete bands. The protein bands are in turn electroblotted onto nitrocellulose, where they are exposed to serum antibodies.¹¹

The genome of HIV codes for the 3 structural proteins typical of retroviruses: the *env* gene codes for the virion surface glycoproteins (and its product includes gp41), the *gag* gene codes for the virion code antigens (and its products include p17, p24, and p55, and the *pol* gene codes for protease, reverse transcriptase, and endonuclease activities (and its products include p31, p53 and p64). In addition, the HIV genome codes for at least 3 other unique proteins. An important consideration is that these gene products may undergo posttranslational modifications including cleavage into 2 or more smaller proteins.

For the licensed WB test, interpretation of reactive and nonreactive tests is based on data from clinical studies submitted to FDA for licensing. The manufacturer states that, for a test to be considered positive for this WB, antibody must be reactive with multiple virus-specific protein bands, i.e. p24 (*gag* protein), p31 (endonuclease component of *pol* [= polymerase] translate), and either gp41 (transmembrane *env* [envelope] glycoprotein) or gp160 (precursors of *env* glycoprotein). If fewer bands are present, the test is considered indeterminate; it is interpreted as negative only if no bands are present on the blot.¹⁰ Figure 2 shows representative patterns of the serum of AIDS patients using the licensed WB test.

We have used the licensed WB for HIV-1 and observed that the serum of 50% of 8 terminal AIDS patients did not have bands at the p24 region thus making the interpretation of the test as "indeterminate", whereas all 4 autopsy serum samples of AIDS cases did have p24 marker. Moreover, none of the terminal AIDS patient

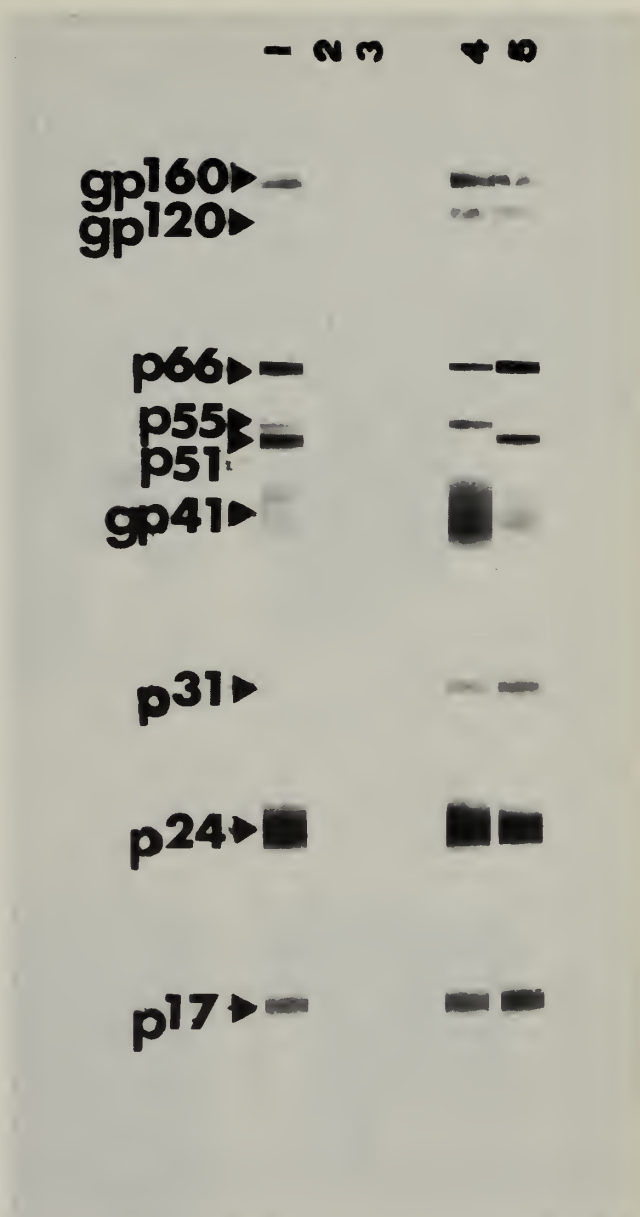


Figure 2. Western blot for the detection of antibodies to HIV-1 utilizing the licensed Biotech/Du Pont kit. The partially purified virus is inactivated by treatment with psoralen and ultraviolet light, and detergent disruption. Specific HIV-1 proteins are fractionated according to their molecular weight by SDS-PAGE and transferred ("blotted") to nitrocellulose which is then washed and blocked to minimize nonspecific immunoglobulin and packaged. The nitrocellulose strips are then reacted as in an ELISA with different serum samples. Visualization of the human immunoglobulin antibodies which bind specifically to the HIV-1 proteins is accomplished *in situ* using a series of reactions with goat anti-human IgG conjugated with biotin, avidin 4-chloro-1-naphthol. Optimal conditions are seen with the serum diluted 1:1,000. If antibodies to any of the major HIV-1 antigens are present in the specimen in sufficient concentration, bands corresponding to the position of one or more of the following HIV-1 proteins (p) or glycoproteins (gp) will be seen on the nitrocellulose strip: p17, p24, p31, gp41, p51, p55, p66, gp120, gp 160.

The numbered strips, represent the following sera:

1. Du Pont strong positive serum.
2. Du Pont weak positive serum.
3. Du Pont negative serum.
4. Centers for Disease Control HIV-1 positive serum control.
5. Cadaver serum from patient who died of AIDS. Note bands to all of the major viral proteins listed above.

sera had detectable antibodies to p55 (Figure 3). Although the sample size is small, we will continue analyzing additional serum samples to see whether these patterns hold. Clinicians should be aware of this pattern of antibody responses interpreted as "indeterminate" in what are clearly terminal AIDS patients.

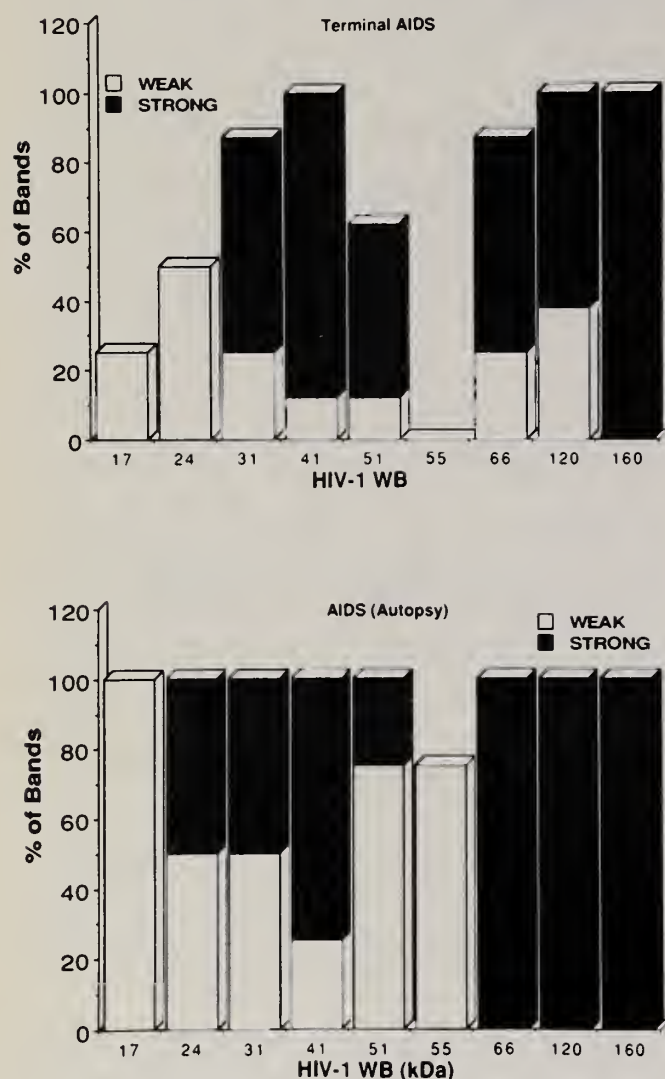


Figure 3. Analysis of Western blot banding patterns to HIV-1 of the serum from patients with terminal AIDS (top graph, n = 8) compared with the serum obtained at autopsy of AIDS cases (bottom graph, n = 4) using the licensed Biotech/Du Pont kit. Note that the serum from terminal AIDS patients often lack antibodies to p17, p24, p51, and (in all cases) p55.

AIDS and Parasitic Infections in Puerto Rico

1. *Pneumocystis Carinii*

Pneumocystis carinii was first described by Carlos Chagas in Brazil in 1909 in smears of the lungs of guinea pigs infected with *Trypanosoma cruzi*. The following year Carini found the same bodies in lung tissue of rats infected with *T. lewisi*. Delanoe and Delanoe, in 1912, found them in Paris rats and gave this presumptive

protozoan its name (others consider this pathogen as an atypical fungus with yeast-like characteristics). *P. carinii* is seen in two forms, trophozoites and cysts, both of which are found in pulmonary alveoli suspended in a matrix of material that, in sections, shows a characteristic honeycomb pattern. The trophozoites are somewhat amoeboid, up to 5 μ in diameter, with a nucleus that is evident on Giemsa- or hematoxylin-stained smears or sections. The cysts are about 5 μ in diameter and have a relatively thick wall when mature, usually contain 8 trophozoites (= intracystic bodies = sporozoites) each with a single nucleus. Typical *P. carinii* cysts in human lung of a patient dying of AIDS is seen in Figure 3. The life cycle usually involves asexual reproduction of free trophozoites which form precysts and thin-walled cysts that mature with the increasing thickness of the cyst wall and the production of the 8 trophozoites.¹²

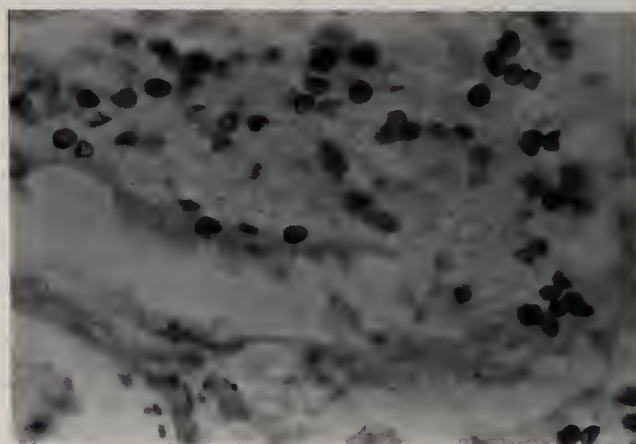


Figure 4. *P. carinii* cysts in human lung of a patient who died of AIDS.

Pneumocystis carinii pneumonia (PCP) occurs both in patients with AIDS as well as in transplant recipients. Since 1980 a high incidence of *Pneumocystis* has also been observed in homosexual males. In the case of individuals with AIDS, PCP infection is often first seen as a 2-3 week prodrome of fever, malaise, and weight loss preceding the onset of pneumonia. Transplant recipients suffer a rapid 24-36 hr onset of pulmonary distress, hypoxia and fever. In both cases, rapid and accurate diagnosis is important. The currently available definitive diagnostic modalities - open-lung biopsy, bronchoscopy with transbronchial biopsy or bronchoalveolar lavage, and/or direct needle biopsy - are invasive and can have significant attendant morbidity and occasional mortality. Jarowenko, *et al.*¹³ found that a combination of very low ELISA antibody titer with a positive or increasing latex particle agglutination antigen titer appeared to be disease-predictive in renal allograft recipients with PCP.

Seroepidemiological studies have shown a high degree of antibody positivity to *P. carinii* in the "normal" human population, thus rendering serology of little value in the diagnosis of cases of active pneumocystosis. These studies were performed by indirect fluorescent antibody (IFA) assay with whole organisms and by enzyme-linked immunosorbent assay (ELISA) with crude lung extracts

used as antigenic preparations. However, Maddison, et al.^{14, 15} found by ELISA that the highest antibody levels occurred in sera from patients with proven or suspected *Pneumocystis* infection, although the range of titers was erratic, possibly because a large number of patients were receiving immunosuppressive therapy. They concluded that the detection of circulating antigen appeared to be most promising as a useful adjunct to diagnosis. Walzer, et al.¹⁶ used subcellular preparations of *P. carinii* from human lung and rats in culture and found by immunoblot that the 40 and 66 kDa antigenic polypeptides were recognized by 6 of 7 AIDS patients but only one of 8 non-AIDS patients having pneumocystosis.

In a report on the first 20 cases (of which 11 were autopsies) of AIDS seen at the Department of Pathology, UPR School of Medicine, the most common infectious agent identified was *Pneumocystis* seen in 15 of the 20 cases. In 12 of the 15 patients, diagnosis had been established before death either by biopsy or cytology.⁶

Climent et al.¹⁷ reported on a case of death caused by *P. carinii* pneumonia in a 6-month old Puerto Rican girl with AIDS whose father was an intravenous drug abuser. However, the source of infection was unknown.

2. *Toxoplasma Gondii*

Toxoplasma gondii is a cosmopolitan parasite of humans and cats. Although discovered in 1908, its complete life cycle was not elucidated until 1970 when the sexual stages were described in cats. *T. gondii* is generally transmitted by the oral route in the form of either oocysts (in soil contaminated by cat feces) or in tissue cysts (in meat) eaten by carnivores. Ultimately, all *Toxoplasma* comes from cats, in which it is a coccidiosis.¹⁸ Toxoplasmosis, the disease caused by *T. gondii*, is observed in only a small portion of immunocompetent, infected individuals. In immunosuppressed individuals, including those with AIDS, cardiac and brain lesions and diseases are common.

Toxoplasmic encephalitis is a major cause of central nervous system infection in patients with AIDS and is in fact the most common parasitic central nervous system manifestation in AIDS. Patients with AIDS and toxoplasmic encephalitis tend to have IgG, but not IgM, anti-*Toxoplasma* antibodies. Moreover, because these patients lack IgM antibody and serial changes in IgG antibody titers, toxoplasmic encephalitis in patients with AIDS is probably due to reactivation of the chronic, latent infection rather than a manifestation of the acute acquired infection.¹⁹ Potasman et al.²⁰ found that 23 of 37 patients with AIDS and toxoplasmic encephalitis had IgG *Toxoplasma* antibody in cerebrospinal fluid compared with none of the patients with AIDS alone. Moreover, they suggested that elevated serum IgG (dye test) antibody titers in patients with evidence of encephalitis may indicate active *Toxoplasma* infection.

The first 100 AIDS autopsies were seen at the Department of Pathology, UPR School of Medicine through December, 1987. Of these 21% had *T. gondii* confirmed in brain and 3% in myocardial tissue (Climent, et al unpublished). In Figure 5, typical *T. gondii* pseudocysts found in the brain of a Puerto Rican patient who died of AIDS are seen.²¹

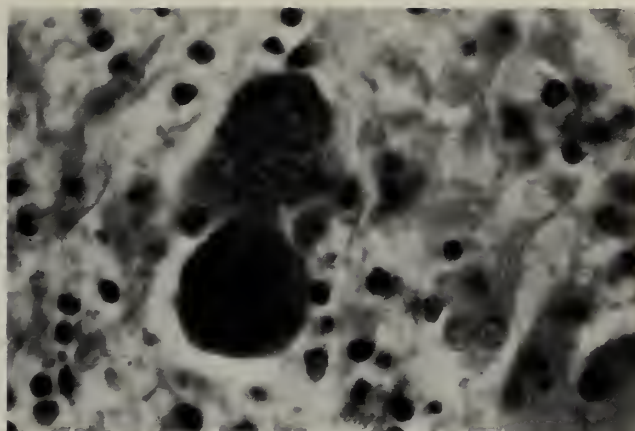


Figure 5. *Toxoplasma gondii* pseudocysts seen in human brain of patient who died of AIDS.

3. *Isospora Belli*

Isospora belli is an opportunistic protozoan pathogen in patients with AIDS. Although it rarely causes diarrhea in patients with AIDS in the United States, isosporiasis has been associated with chronic watery diarrhea and weight loss in 15% of AIDS patients in Haiti. A key point is that the chronic watery diarrhea and weight loss seen is clinically indistinguishable from disease caused by *Cryptosporidium*. Isosporiasis in those patients with AIDS responded to therapy with trimethoprim-sulfamethoxazole, but was associated with a high rate (47%) of recurrence.²² Parasitologic diagnosis is accomplished by the identification of the unsporulated oocysts in feces which are approximately 4x larger than the sporulated oocysts of *Cryptosporidium* (see below).

In May 1985, a 31-year old Puerto Rican man with severe intractable diarrhea of 5 months duration in which he lost 89 pounds was found to have *Isospora belli* oocysts in his stool. He died the following month and at autopsy no *I. belli* was found in tissue sections. However, at autopsy, this patient was found to have intestinal strongyloidiasis and intestinal schistosomiasis due to infection with *S. mansoni*, as well as *P. carinii* pneumonia.²³

4. *Cryptosporidium*

Cryptosporidium is a protozoan parasite which completes its life cycle in the microvillous border of the intestinal and respiratory surface epitheliums of mammals, birds, and reptiles. The parasite responsible for cryptosporidiosis of humans and his domesticated mammals (*C. parvum*) exhibits little or no host specificity and may infect a variety of tissues. For many years the infection was thought to be uncommon and the organism was thought to be opportunistic and, like the other coccidia, highly host specific. It is now known that *Cryptosporidium* has little or no host specificity, and that it is transmitted by ingestion of oocysts that are fully sporulated and infective at the time they are passed in the feces. Parasitologic diagnosis is accomplished by the identification of the small (ca. 5 μ) sporulated oocysts in feces.

In humans, *Cryptosporidium* causes short-term, flu-like gastrointestinal illness in immunocompetent persons and severe, persistent, life-threatening, cholera-like diarrhea in immunodeficient individuals. Diarrhea in many of these immunodeficient patients often becomes irreversible and the fluid loss is excessive, with 3 to 6 liters per day being common and as many as 17 liters per day before death have been recorded.²⁴

Calves are a source of human infection, and it has been suggested that companion animals such as rodents, puppies, and kittens are also reservoir hosts making this a zoonosis. However, zoonotic transmission does not explain the large number of infections among urban dwellers where exposure to animal feces is minimal, and evidence has been accumulating rapidly that person-to-person transmission of cryptosporidiosis is common. Direct transmission may occur during sexual practices involving oral-anal contact. Indirect transmission may occur by exposure to fecally contaminated environmental surfaces, food, and water.²⁴

Human infection with *Cryptosporidium* is extremely rare in P.R. In our Department of Pathology only two cases have been seen. The *Cryptosporidium* was identified in the stools pre mortem. However, at autopsy no *Cryptosporidium* was found in the two AIDS cases (one each in 1985 and 1986). The cause of death in both cases were other nonparasitic opportunistic infections.

5. *Schistosoma Mansoni*

Schistosoma mansoni, an intravascular parasitic trematode, was first described in humans in Puerto Rico in 1904 by I. González Martínez. Some 40 years later, a parasitologic survey of Selective Service registrants in which 1 g of feces was examined revealed a prevalence of almost 10%. In 1953, a similar parasitologic survey of students revealed a 10% prevalence (reviewed in ref. 25). Since that time, no island wide, systematic, parasitologic survey has been done.

Definitive parasitologic diagnosis of infection with *S. mansoni* is routinely done by the examination of a measured amount of feces, the modified Ritchie formol-ether concentration method being the most sensitive since it uses 1 g of feces.^{26, 27} However, there are now excellent defined antigen/test systems for the serodiagnosis of infection, although they do not define intensity of infection.²⁸ A simple microprecipitin test using whole *S. mansoni* eggs, called the circumoval precipitin (COP) test has been found to have high (>95%) sensitivity and specificity.²⁹ A typical COP reaction using the serum of a patient with AIDS and *S. mansoni* is seen in Figure 9.

Ectopic granulomatous lesions due to *S. mansoni* in immunocompetent individuals have been reported in many organs of the body, and are often found in heavily infected individuals.^{30, 31} However, there are few reports on immunosuppressed individuals in which the granuloma formation has been abrogated. Hillyer and Cangiano,³² found that a renal transplant patient kept on maintenance immunosuppression consisting of prednisone and azathioprine had *S. mansoni* eggs in the liver and colon, but with no granulomatous response around them. A 37-year old Puerto Rican man with a history of

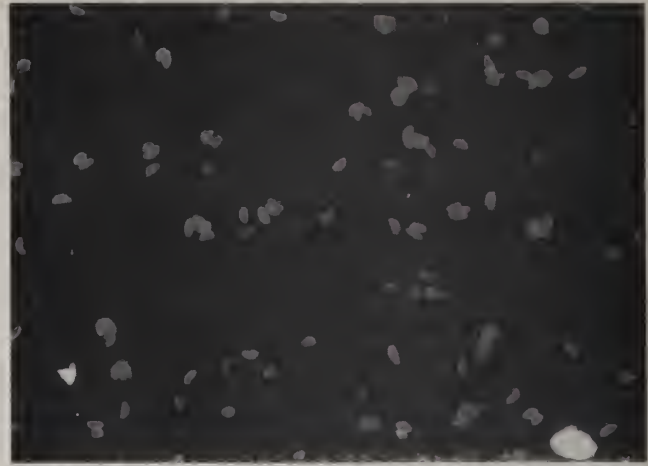


Figure 6. Indirect fluorescence of the serum of a patient with AIDS demonstrating antibodies to *T. gondii* tachyzoites at a 1:1024 serum dilution. Note the brilliant fluorescence indicating high titer antibodies.

intravenous drug abuse for 20 years and with AIDS died of cardiorespiratory arrest. At autopsy he was found to have disseminated infection with *Schistosoma mansoni* (eggs) involving lung, liver, spleen, intestine, pancreas, and testis. This same patient also had *T. gondii* meningo-encephalitis.²¹ The *S. mansoni* eggs of this patient lacked the typical delayed-type hypersensitivity granulomatous reactions seen in immunocompetent and infected individuals (Figures 7, 8). Of the first 100 autopsies of AIDS cases seen at our Department of Pathology, UPR School of Medicine, 7 had *S. mansoni* eggs in tissues, all were males 28-39 years old, and 5 were drug addicts (Climent, *et al.*, in prep.).

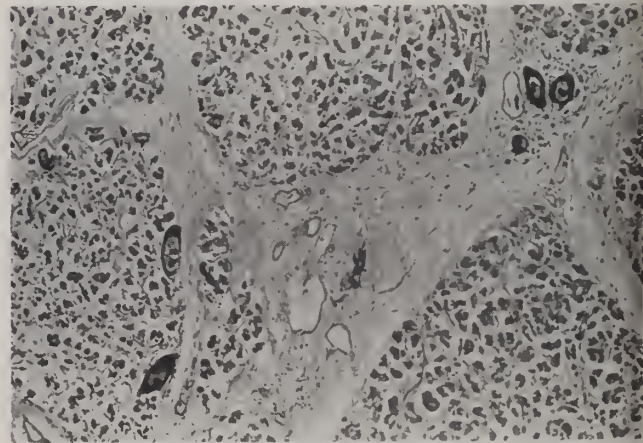


Figure 7. *Schistosoma mansoni* eggs in pancreatic tissue of patient who died of AIDS. Note absence of the delayed hypersensitivity granulomatous response indicating absence of cellular immune response to the egg of the parasite.

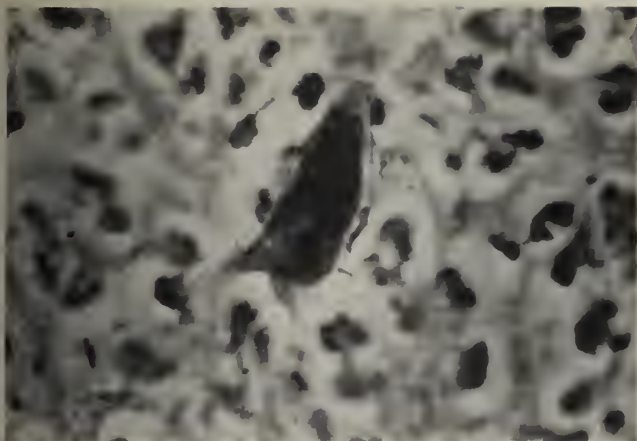


Figure 8. Higher magnification demonstrating *S. mansoni* egg in pancreas of patient who died of AIDS. Note the absence of granulomatous response around the egg.



Figure 9. Circumoval precipitin reaction of cadaver serum from a patient who died of AIDS and also was infected with *S. mansoni*. Note presence of small blebs indicating the presence of antibodies.

6. Strongyloides Stercoralis

Little is known about the current prevalence of human strongyloidiasis in Puerto Rico, although it is a commonly expressed concern in the local transplant program. *Strongyloides* differs from many of the other parasitic helminths in that they can undergo a succession of generations within their host in the absence of external infection. In this manner patients may die of a fulminating disease long after their initial infection, often accompanied by gram-negative septicemia.³³ Although *Strongyloides* is not associated with AIDS, human infection is found in Puerto Rico and has to be suspected as a factor when diarrhea complicates any severe illness. Diagnosis is done by identifying the typical larvae in feces. Of the first 100 autopsies done at the Department of Pathology, UPR School of Medicine, 3 had intestinal, not disseminated, strongyloidiasis (Climent, *et al.* in preparation).

In conclusion, it is obvious that in Puerto Rico there is a need to evaluate the immune response patterns of AIDS patients both to HIV-1 and to the relevant parasitic infection in order to validate and use the immune response as an aid for the diagnosis and prognosis of these patients.

Resumen: En Puerto Rico, desde que se hizo el primer diagnóstico de SIDA en 1981, el número de casos y muertes ha ido aumentando progresivamente de 1,253 casos y 741 muertes en mayo 1988 a 1,526 casos y 900 muertes en agosto 2, 1988. En Estados Unidos la mayoría de los casos se diagnostican en varones homosexuales o bisexuales. En Puerto Rico, la mayoría de los casos de SIDA ocurren en varones, heterosexuales y adictos a drogas intravenosas. Las infecciones por parásitos son frecuentes en los pacientes con SIDA en Puerto Rico. Las infecciones parasitarias que se observan con mayor frecuencia son pulmonía por *P. carinii* y meningoencefalitis por *Toxoplasma gondii*. Otras menos frecuentes son infección por *Schistosoma mansoni* y *Strongyloides stercoralis*. También se ha visto un caso de infección por *Isospora belli* y dos por *Cryptosporidium*. Estos diagnósticos se hicieron premortem y en la autopsia no se pudieron identificar estos organismos.

Este artículo revisa el estado actual de las infecciones por estos parásitos y su diagnóstico en relación con los pacientes de SIDA en Puerto Rico.

Acknowledgements

These investigations were supported by the Parasitic Diseases Research Program of Puerto Rico through NIH Grant No. RR-2657. The technical and photographic assistance of Enid Castillo, Maricelis Soler de Galanes, Noemí Rosado, Gisella Battisti, and Román Vélez is warmly acknowledged.

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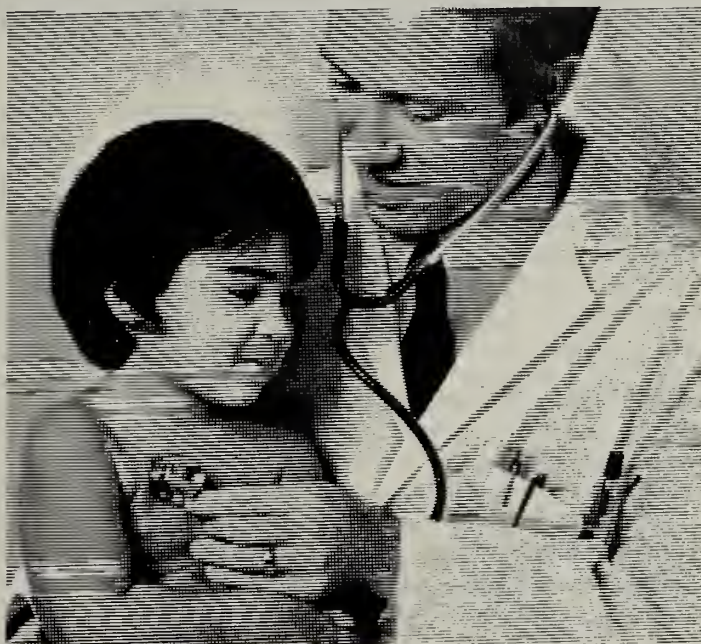
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FORO DE MEDICINA DEPORTIVA

El Uso y Abuso de Sustancias Prohibidas en el Deporte

Walter R. Frontera, MD, PhD
Luis R. Colon Rivera, MD

El uso y abuso de sustancias prohibidas en el deporte es un problema de gran complejidad que tiene sus orígenes en la Grecia antigua.^{1, 2} Se dice que en el tercer siglo antes de Cristo los competidores en las antiguas olimpiadas griegas utilizaban hierbas y hongos para mejorar su ejecutoria.¹ Desde la segunda mitad del siglo XIX se ha documentado en uso de diversas sustancias tales como nitroglicerina, estricnina, amfetaminas, esteroides anabólicos, cafeína y otras en varias competencias deportivas.^{1, 2} Ya en el siglo XX, y en la década de los 60 varios atletas murieron como resultado directo del uso de sustancias prohibidas.³ En 1965 los gobiernos de Bélgica y Francia aprobaron varias leyes en un intento por solucionar el problema. Más tarde, en 1967, el Comité Olímpico Internacional (COI) creó una Comisión Médica (CM-COI) la cual tiene como una de sus responsabilidades principales establecer la lista de sustancias prohibidas y el reglamento que controla el uso de dichas sustancias en el deporte.² En los últimos años, varias naciones, incluyendo Canadá y los países Escandinavos, han establecido programas de detección, no sólo durante las competencias sino también durante las etapas de entrenamiento, y realizan pruebas al azar durante todo el año.⁴

Aunque reconocido por muchos como una situación seria y difícil, existe gran confusión entre los profesionales de la salud sobre este problema. El propósito de este escrito es el de presentar y discutir varios aspectos fundamentales del uso y abuso de sustancias prohibidas en el deporte y desde cuál perspectiva debe enfrentarse.

Origen del Problema

Las razones por las cuales un atleta utiliza sustancias prohibidas puede ser diversas. El éxito en la competencia deportiva es percibido por el atleta como un medio para obtener reconocimiento, popularidad y grandes beneficios materiales. La posibilidad de mejorar el rendimiento en la competencia y alcanzar el éxito deseado, estimula al competidor a utilizar sustancias que han sido prohibidas por sus posibles efectos psico y/o ergotrópicos (ergo=trabajo; trópico=cambiar). Mas aún, el reconocer que

muchos compañeros atletas utilizan dichas sustancias, puede estimular su uso entre aquellos que no las utilizan, si éstos últimos interpretan estar en desventaja. En segundo lugar, la falta de información puede contribuir a que los deportistas subestimen los peligros del uso y abuso de dichas sustancias. Finalmente, no debemos olvidar que los deportistas son parte de nuestra sociedad. El problema que discutimos en este artículo puede ser el reflejo de una sociedad donde los ciudadanos utilizan sustancias químicas sin control para enfrentar cualquier situación difícil o "disfrutar" de emociones de euforia o sedación, logros o premiación superficial o pasajera.

"Dopaje"

A. Definición

El término "dopaje" ("doping") es una expresión popular que se refiere al uso y abuso de sustancias prohibidas en el deporte. Prokop³ y Hanley⁴ sostienen que dicho término se originó en Africa del Sur donde se le daba el nombre de "dop" a una bebida utilizada por los nativos que contenía alcohol, extracto de nueces y xantinas.

La CM-COI define "dopaje" como la administración o el uso por un atleta competidor de cualquier sustancia fisiológica utilizada en cantidades anormales o por una vía anormal de entrada al cuerpo, con la única intención, de mejorar de forma artificial e injusta, su ejecutoria en la competencia.^{5, 6} También se considera "dopaje", cualquier tratamiento médico con una sustancia que por sus efectos sea capaz de mejorar el rendimiento de un atleta en competencia de manera artificial e injusta; aún cuando dicho tratamiento sea necesario.

B. Clasificación de Sustancias Prohibidas

La Tabla I presenta la clasificación de las sustancias prohibidas. La Tabla II presenta ejemplos específicos de varias sustancias incluidas en las clases farmacológicas de "dopaje". La Tabla III presenta ejemplos de varias sustancias cuyo uso está permitido para fines terapéuticos por la CM-COI. En este artículo, no es posible discutir en detalle la farmacología de todas estas sustancias y el efecto que pueden tener cada una de ellas en el rendimiento de un atleta. Sin embargo, es impor-

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tante hacer algunas observaciones sobre los diversos tipos de sustancias y métodos prohibidos.

Tabla 1

Clasificación de Sustancias Prohibidas por la Comisión Médica del Comité Olímpico Internacional

1. Clases farmacológicas de "dopaje"

- A. Estimulantes
- B. Narcóticos
- C. Esteroides anabólicos
- D. Bloqueadores-beta
- E. Diuréticos

2. Métodos de "dopaje"

- A. Transfusión de sangre ("blood doping")
- B. Manipulación farmacológica, química y/o física.

3. Sustancias sujetas a algunas restricciones

- A. Alcohol
- B. Anestésicos locales
- C. Corticoesteroides

Clases Farmacológicas

Los estimulantes son utilizados por los atletas por sus efectos sobre el sistema nervioso central alterando la percepción del cansancio. Cabe mencionar que esta alteración puede aumentar el riesgo de sufrir lesiones musculoesqueléticas.⁷ Aparte de los cambios psicológicos de estimulación, la modificación de la atención y concentración y de los efectos fisiológicos y metabólicos que afectan la ejecutoria de un atleta, los estimulantes tienen acciones secundarias que pueden resultar en un comportamiento agresivo, ansiedad, paranoia, depresión, anomalías en el ritmo cardíaco, aumento de la presión sanguínea, hipertermia, fallo cardíaco y muerte. Muchas de las sustancias en este grupo, por ejemplo las aminas simpatomiméticas, están presentes en varios medicamentos utilizados en el tratamiento de problemas de salud comunes como lo son el catarro, las alergias y otros. Debido a que éstos se obtienen sin receta, el atleta debe ser advertido de no consumir ningún medicamento sin antes asegurarse de las sustancias contenidas en los mismos. Es importante apuntar que la cafeína está incluida en este grupo. La cafeína disminuye la sensación de cansancio, tiene un efecto lipolítico que favorece el metabolismo de ácidos grasos (fuente vital de energía durante los eventos deportivos de larga duración) y aumenta la contractilidad del músculo esquelético.^{8, 9}

Los narcóticos analgésicos pueden producir una sensación de euforia y la ilusión de ser invencible. El atleta puede percibir seguridad en situaciones peligrosas que aumentan el riesgo de lesiones. Además, esta categoría de drogas aumenta el umbral de dolor-síntoma importante y produce dependencia psicológica y fisiológica. La Tabla III presenta alternativas para el tratamiento de lesiones atléticas que requieren analgésicos y/o anti-inflamatorios.

Tabla 2

Ejemplos de Drogas y/o Sustancias Prohibidas por Categoría *

A. Estimulantes

Genérico	Ejemplos
amfetamina	Benzedrine; Dexedrine
cafeína †	colas; Empirin; Anacin
cocaína	-----
efedrina	Rynatus; Primatene
fenilefrina	Coricidin; Dristan
fenilpropanolamina	Sinutab; Contac
isoproterenol	Isuprel
metaproterenol	Allupent
metoxifenamina	Ritalin
seudoeferina	Actifed; Co-tylenol; sudafed
y otras sustancias relacionadas	

B. Narcóticos

codeína	-----
diamorfina	heroína
morfina	Duromorph
oxocodona	Percodan
oxomorfina	Narcan
pentazocina	Talwin
trimeperidina	Demerol
tintura de opio	Paregorico
y otras sustancias relacionadas	

C. Esteroides Anabólicos

metandiedona	Dianabol
metiltestosterona	Estratest; Oreton
nandrolona	Durabolin
oximesterona	Oranabol
testosterona ‡	Oreton
y otras sustancias relacionadas	

D. Bloqueadores beta

atenolol	Tenormin
metoprolol	Lopressor
nadolol	Corgard
propranolol	Inderal
timolol	Blocadren
y otras sustancias similares	

E. Diuréticos

acetazolamida	Diamox
clortalidona	Hygroton
furosemida	Lasix
hidroclorotiazida	Oretic
espironolactona	Aldactone
triamtereno	Dyazide
y otras sustancias similares	

* Por la limitación de espacio es imposible incluir una lista más completa. Este cuadro solo presenta ejemplos; una lista más extensa puede obtenerse escribiendo a los autores.

† Se considera positivo si la concentración en la orina es mayor de 12 mcg/ml.

‡ Se considera positivo si la razón testosterona/epitestosterona en orina es mayor de 6.

Tabla 3

Ejemplos de Sustancias No-Prohibidas *

- A. Analgésicos
 - aspirina
 - acetaminofen
- B. Antiasmáticos (solo en aerosol)
 - Intal (cromolyn)
 - Proventil y Ventolin (albuterol)
 - Brethine (terbutaline)
- C. Antibióticos (todos)
- D. Antidiarréicos
 - Kaopectate
 - Lomotil
 - Pepto-bismol
- E. Antihistamínicos
 - Benadryl
 - Chlor-trimétron
 - Seldane
- F. Antiinflamatorios
 - Clinoril
 - Feldene
 - Indocin
 - Motrin
 - Naprosyn
- G. Descongestionantes
 - Afrin
 - Sinex
- H. Laxantes (todos)
- I. Medicina para la tos (no-narcóticos)
 - dextromethorphan
- J. Medicina para uso ótico y oftálmico (uso tópico aceptable)
- K. Relajantes musculares
 - Flexeril
 - Norflex
 - Parafon
 - Soma

* Por limitaciones de espacio el cuadro solo presenta varios ejemplos y no pretende ser una lista completa. Una lista más extensa puede obtenerse escribiendo a los autores.

El uso de esteroides anabólicos androgénicos (EAA) para mejorar el rendimiento durante la competencia es una forma relativamente reciente (su uso comenzó en la década de 1950) y diferente de abuso de sustancias. Los EAA son utilizados en deportes como levantamiento de pesas, atletismo (lanzamiento de la pesa, martillo entre otros) y boxeo con el propósito de estimular la síntesis de proteínas y aumentar la masa y fortaleza muscular.¹⁰ La efectividad de los EAA es motivo de controversia en la literatura científica y varios autores opinan que estas sustancias aumentan el tamaño y la fortaleza muscular sólo en atletas experimentados en el entrenamiento de alta intensidad.^{10, 11} Su uso en deportes donde predomina el metabolismo oxidativo, como la maratón y el ciclismo de ruta, se basa en un posible aumento en la formación de células rojas que podría favorecer el transporte de oxígeno.¹¹ Sin embargo, no hay evidencia clara de que los EAA mejoren el rendimiento en deportes que dependen de una alta capacidad aeróbica.

Los EAA están prohibidos no sólo porque su uso viola los principios olímpicos de la sana competencia, sino también por sus efectos secundarios adversos a la salud del atleta. En el hombre, estas sustancias pueden resultar en disfunción renal, atrofia testicular, reducción en la

espermatogénesis, hipertrofia de la próstata, calvicie prematura, acné y daño hepático. Además, los EAA causan cierre prematuro de las epífisis óseas en los adolescentes y masculinización acompañada de alteraciones en la función reproductiva de la mujer. También pueden producir agresividad, irritabilidad, depresión y cambios de personalidad.

Los bloqueadores beta son utilizados por atletas en los deportes de tiro con arco, esgrima y tiro, para reducir la ansiedad y estabilizar el dedo del gatillo (similar al efecto en pacientes con temblores —“essential tremor”— o con miedo a ejecutar frente a una audiencia —“stage fright”). Además, al reducir la frecuencia cardíaca, prolongan el tiempo para que el atleta ejecute el disparo sin coincidir con la contracción del miocardio.¹² Es importante señalar que dichas sustancias inhiben la lipólisis y la glucogenólisis; ambos mecanismos metabólicos de producción de energía durante los eventos de larga duración (maratón y otros).¹³ De esta forma pueden disminuir el rendimiento del atleta en estos eventos.¹⁴

Los diuréticos son utilizados por atletas que participan en deportes donde se compite por categorías de peso (boxeo, lucha olímpica y otros). La pérdida de líquido, sin embargo, está asociada a una disminución en la fuerza y tolerancia muscular¹⁵ que afecta negativamente el rendimiento del deportista. Algunos atletas utilizan los diuréticos para reducir la concentración en orina de otras sustancias prohibidas, en un intento por minimizar su detección.

Métodos de “Dopaje”

Uno de los métodos utilizados por los atletas en los últimos veinte años para manipular el rendimiento durante la competencia es el llamado “dopaje” por transfusión de sangre o “blood doping”. Esta técnica consiste en la remoción de 0.5 a 1.0 litros de sangre varias semanas antes de la competencia, el almacenamiento a bajas temperaturas de las células rojas y la reinfusión pocos días antes del evento. Gledhill¹⁶ sostiene que dicho procedimiento resulta en un aumento en la concentración de hemoglobina, el contenido de oxígeno en la sangre arterial, el consumo máximo de oxígeno y el rendimiento en eventos donde predomina el metabolismo aeróbico. Este tipo de manipulación artificial viola los principios olímpicos y debe considerarse peligrosa si tomamos en consideración los riesgos de una transfusión de sangre. Desafortunadamente no existe una prueba de laboratorio fidedigna para detectar su uso.

Incluidos también en esta categoría están las sustancias y/o métodos que alteran la integridad y validez de las muestras de orina. Ejemplos de estos métodos son la sustitución de la orina, la adición de sustancias (por ejemplo: agua, detergentes) para cambiar la gravedad específica, el pH y la temperatura de la orina y los compuestos que pueden inhibir la excreción renal de las sustancias prohibidas como por ejemplo el probenecid.

Sustancias sujetas a algunas restricciones

Ciertas sustancias están supeditadas a algunas restricciones. El etanol (alcohol etílico), a pesar de no estar prohibido, puede incluirse en las pruebas de detección si una Federación Deportiva Internacional así lo solicita.

Los anestésicos locales (procaína, xilocaína y carbo-caína) pueden ser utilizados de forma local o intraarticular si existe justificación médica; la CM-COI debe ser notificada por escrito del diagnóstico, dosis y método de administración. Finalmente, los corticosteroides pueden utilizarse de forma tópica (uso dermatológico, oftálmico y ótico), en terapia de inhalación (asma, rinitis alérgica) y en inyecciones locales o intraarticulares, pero no por vía intramuscular o endovenosa. Al igual que en el caso de los anestésicos, la CM-COI tiene que ser notificada por escrito si fuera necesario utilizar corticosteroides inyectables (vía local o intraarticular).

Es importante señalar que muchos de las sustancias prohibidas pueden ser adquiridas fácilmente por los atletas pues no son ilegales ni requieren la autorización de un médico. Por el contrario, algunas sustancias ilegales no están prohibidas por la CM-COI pues no ha sido comprobado científicamente que mejoren el rendimiento de un atleta. Un ejemplo de esto es la marihuana, cuyo ingrediente activo, el tetrahidrocannabinol, altera la percepción del tiempo, disminuye la percepción de la profundidad, resulta en un deterioro de la memoria reciente y produce euforia y relajación. Además, evidencia reciente sostiene que su uso prolongado puede tener serias consecuencias fisiopatológicas sobre diversos sistemas.¹⁷ La no inclusión de la marihuana en la lista de sustancias prohibidas no constituye una licencia para que sea utilizada por los deportistas. Esta exclusión es más bien, un reflejo de la diferencia entre la manipulación artificial de la ejecutoria de un atleta y la problemática de las sustancias ilegales y su uso o abuso.

C. Frecuencia de uso entre los atletas

La Tabla IV presenta la frecuencia de resultados positivos para dos categorías de sustancias prohibidas durante los Juegos Olímpicos (Invierno y Verano) desde 1968 y los Juegos Panamericanos celebrados en 1983.¹⁸ Durante 1986, los laboratorios acreditados por la CM-COI, localizados en varios países del mundo, realizaron un total de 32,932 pruebas.¹⁹ El 2.1% y 1.7% de las muestras tomadas durante actividades de entrenamiento y competencias respectivamente resultaron positivas.¹⁹ Entre las muestras informadas como positivas, 63.9% fueron

EAA, 25.8% contenían estimulantes, 4.5% reflejaron bloqueadores beta, 3.3% demostraron narcóticos y 2.2% y 0.3% contenían sedantes y diuréticos respectivamente. Estos resultados sugieren que, a nivel internacional, el problema de uso de sustancias prohibidas en el deporte no radica en las drogas ilegales (heroína, cocaína), sino en sustancias como los EAA. Debe señalarse que no se han estado realizando pruebas para marihuana.

De la discusión sobre la frecuencia de uso entre atletas surge la interrogante de si el problema de uso y abuso de sustancias prohibidas en el deporte es un espejo de la vivencia social que lo rodea. Cabe preguntarse cuál es la prevalencia de uso y abuso en grupos o sub-grupos de la sociedad general, comparada con la prevalencia de uso y abuso en el deporte.

¿Es el deporte una actividad que protege al que lo practica del uso y abuso de sustancias prohibidas?

Detección

Las primeras pruebas oficiales para detectar el uso de sustancias prohibidas en el deporte fueron realizadas en Europa a comienzos de la década de 1960 en varias competencias de ciclismo.² La CM-COI realizó pruebas preliminares en los Juegos Olímpicos de 1968 pero no fue hasta 1972, durante los Juegos Olímpicos de Verano en Munich, que se instituyó un programa formal de detección en competencias olímpicas internacionales.² Durante los Juegos Olímpicos de 1976 en Montreal se incluyeron pruebas para detectar el uso de EAA. En años subsiguientes y para los Juegos Olímpicos de 1984 en Los Angeles se incluyó la cafeína. En mayo de 1985, la CM-COI añadió los bloqueadores beta y la transfusión de sangre a la lista de sustancias prohibidas. Finalmente, en marzo de 1988 se añadieron las sustancias y/o métodos que alteran la integridad y validez de la orina. A pesar de que la epidemiología del problema no ha sido estudiada cuidadosamente, varias naciones, incluyendo Canadá y los países Escandinavos, han establecido programas de detección que cubren no sólo las competencias sino las etapas de entrenamiento. En Suecia y en Finlandia se realizaron 2,000 y 900 pruebas al azar respectivamente en 1985.⁴

El proceso de detección comienza con la toma de una muestra de orina. Para evitar la adulteración de la muestra, la CM-COI recomienda que el atleta seleccionado (la selección depende en la mayoría de las competencias internacionales del resultado de la competencia) sea acompañado en todo momento, incluyendo al momento de dar la muestra, por un oficial del programa.^{6, 18} El pH, la temperatura y la gravedad específica pueden ser determinados si es deseable comprobar que la muestra no ha sido diluida o adulterada con otras sustancias.^{6, 18} La muestra es identificada con un número, transportada al laboratorio bajo la custodia de un oficial del programa y sometida al análisis correspondiente por el personal del laboratorio quien desconoce la identidad del deportista.

Todas las pruebas de detección en orina se basan en los principios de metabolismo y excreción de compuestos

Tabla 4

Frecuencia de Resultados Positivos en Juegos Olímpicos de Invierno y Verano y Juegos Panamericanos de 1983

Año	Ciudad	Estimulantes		Anabólicos	
		total muestras	positivos	total muestras	positivos
1968	Grenoble	86	0	-	-
	México	667	1	-	-
1972	Saporo	271	1	-	-
	Munich	2,079	7	-	-
1976	Insbruck	390	2	-	-
	Montreal	1,986	3	275	8
1980	Lake Placid	440	0	350	0
	Moscú	1,645	0	831	0
1983	Caracas	825	4	825	15
1984	Sarajevo	424	0	325	1
	Los Angeles	1,507	1	1,507	11

químicos y/o sus metabolitos.²⁰ Los métodos utilizados en la identificación de estas sustancias son de dos clases: inmunológicos y químicos. El método inmunológico (por ejemplo el radioinmuno ensayo) hace uso de un anticuerpo específico para la sustancia. El método químico (cromatografía de capa fina, cromatografía de gas) se basa en la comparación de las propiedades químicas y físicas de la sustancias con una sustancia conocida.

Las pruebas se realizan en dos pasos: una prueba de cernimiento y una prueba confirmatoria si en la primera se detectara una sustancia prohibida. Los métodos de cernimiento, aunque carecen de especificidad, son altamente sensitivos pues detectan cantidades pequeñas de las sustancias. Los métodos analíticos seleccionados para la confirmación son tanto altamente sensitivos como específicos. Sin embargo, es importante señalar que a pesar de la sofisticación de los métodos, esto no son infalibles.²¹

La CM-COI acepta la combinación de la cromatografía de gas y la espectrometría de masa ("GC-MS") como el único método para el análisis de confirmación. En síntesis, el método de GC-MS separa inicialmente los componentes de una mezcla por cromatografía de gas (desplazamiento diferencial en un sistema de dos fases). Luego los introduce uno por uno en el espectrómetro de masa donde cada compuesto es fragmentado en los iones específicos que lo componen. El patrón de abundancia relativa de estos fragmentos es, en efecto, un espectro de masa o "huella molecular" de la sustancia. La identificación es posible por la comparación computadorizada con patrones estándares. Con la excepción de la cafeína y la testosterona el análisis se considera positivo si se detecta la presencia de una sustancia prohibida. En el caso de la cafeína y la testosterona es necesario un análisis cuantitativo (ver notas de Tabla II).

El Programa Control de "Dopaje": Enfoque Biosicosocial

Con lo discutido anteriormente sirviéndonos de fundamento, debemos pasar a examinar los aspectos esenciales de un programa efectivo de control del "dopaje". Lo primero que deseamos distinguir es que el uso y abuso de drogas y sustancias prohibidas en el deporte es tanto una práctica - que por ser engañosa debe ser rechazada — así como un problema de salud - que como problema debe ser estudiado y tratado a fondo. Una segunda distinción, consiste en que el estudiarlo y tratarlo debe hacerse desde la perspectiva del modelo biopsicosocial de la medicina.²² Desde esta perspectiva, un programa de control del "dopaje" se divide en dos partes: una preventiva y otra terapéutica y rehabilitadora.

A. Enseñanza - Prevención

Un programa efectivo de enseñanza y prevención respecto al uso y abuso de sustancias prohibidas en la práctica del deporte tiene que partir de la premisa de que esta conducta impropia es producto de la presión social,²³ la curiosidad asociada con la ignorancia y las falsas imágenes que se promueven para producir falsos rendimientos.^{24, 25} Dicha conducta es, en verdad, un espejo que refleja la frágil identidad individual y colectiva de la

sociedad moderna. El deporte no es excepción en este sentido. Así como el deporte es un medio para fomentar la vida sana, así también se ha convertido, reflejando a la sociedad, en escenario de conflictos disociadores y antisociales, donde el fin de la victoria justifica los medios utilizados para alcanzarla.

Como ha quedado demostrado por Robinson y su grupo,²⁵ el modelo de resistencia social intensa, con amplia difusión a todos los niveles enseñanza e institucionales; con la estrecha colaboración de los medios de información (prensa, televisión y radio); y con la participación de figuras de modelaje positivo en lo individual y en lo colectivo, ofrece la mejor alternativa para la prevención temprana del uso y abuso de sustancias. Esta alternativa requiere la identificación de poblaciones con factores de riesgo asociados^{24, 25, 27} tales como:

- 1) jóvenes en desventaja socio-económica, muchas víctimas de abuso;
- 2) familias con historial de problemas adictivos o trastornos emocionales;
- 3) niños con problemas de aprendizaje, depresión o ansiedad;
- 4) personas con carencia de apoyo familiar-comunicativo y falta de destrezas sociales.

Además de identificar las poblaciones a riesgo, hay que tener conciencia de que en el deporte, se proyectan los miedos, la omnipotencia, las frustraciones, el aburrimiento, la dependencia, la pobre autoestima, la falta de voluntad y los grandes contrastes entre la euforia de ganar y el dolor de perder. Para saber ganar y/o perder, se necesita una personalidad segura y estable, una familia sana y una sociedad saludable, equitativa y justa. El modelo de resistencia social incluye,^{23, 26, 28, 29} además:

1. enseñanza sobre las consecuencias sociales y sobre la salud, que conlleva el uso y abuso de sustancias;
2. mensajes que desalienten el patrón de uso y abuso;
3. el establecimiento de metas claras para combatir el problema día a día.

B. Tratamiento y Rehabilitación

El concepto de rehabilitación reconoce el problema de uso y abuso de sustancias como un problema de salud. La rehabilitación implica restituir algo a su funcionamiento óptimo natural. Es un proceso complejo y prolongado en el que se identifica, se enseña y se provee tratamiento —que incluye, entre otros, consejería, confrontación, clarificación, modelaje y dirección— para reincorporar al individuo a la vida saludable. El proceso de rehabilitación está descrito por las siguientes etapas:

- 1) aceptación y compromiso longitudinal con el tratamiento;
- 2) acatamiento de las normas y requisitos del programa rehabilitador;
- 3) abstinencia del uso de sustancias prohibidas y
- 4) ajuste social con reorientación de su personalidad moral-social y la recuperación de la salud física y mental.

Cabe destacar que la rehabilitación pone a prueba la voluntad, la resistencia, la motivación, la perseverancia y el apoyo, tanto del que va a ser rehabilitado, como de quien rehabilita. Se da bajo la influencia de grandes tensiones y esfuerzos, físicos y mentales.

En síntesis, el problema de uso y abuso de sustancias en el deporte, tiene que ubicarse en el contexto más amplio del modelo biopsicosocial de la medicina. El uso y abuso de sustancias prohibidas en el deporte viola los principios fundamentales del olimpismo y de la sana competencia deportiva. Los reglamentos de "dopaje" en el deporte, así como el código de sustancias controladas vigente en el país, ubican el uso y abuso de sustancias como un problema que, como profesionales de la salud, nos corresponde estudiar y contribuir a su posible solución.

Resumen: Se han presentado y discutido las definiciones, clasificaciones y ejemplos específicos de sustancias prohibidas y no prohibidas en el deporte. Se discutió el problema de la detección de sustancias y el papel de los laboratorios y las metodologías usadas en la detección. Finalmente, se trató el asunto de la prevención, el tratamiento y la rehabilitación desde la perspectiva del modelo biopsicosocial de la medicina.

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¿Qué es el Centro de Salud Deportiva y Ciencias del Ejercicio?

El Centro de Salud Deportiva y Ciencias del Ejercicio (SADCE), surge de la iniciativa conjunta del Comité Olímpico de Puerto Rico y el Recinto de Ciencias Médicas de la Universidad de Puerto Rico que, unidos, colaboran en un convenio innovador para proveer al pueblo puertorriqueño de un escenario que contribuya al mejor desarrollo integral (físico, psicológico y social) de la salud.

Los servicios organizados y ofrecidos por este Centro tienen como prioridad la promoción y el mantenimiento de la salud como un concepto dinámico en el que se aspira a optimizar la calidad de vida.

Para cumplir con este objetivo general, se educará a la comunidad, incluyendo a los atletas, así como a la población general, sobre los beneficios que conllevan el ejercicio y la actividad deportiva. Es por esto que SADCE estimula el desarrollo de la docencia, la evaluación y la investigación científica desde la perspectiva interdisciplinaria de las profesiones aliadas a la Salud Deportiva.

Este taller de trabajo brinda servicios de asistencia a diferentes niveles de intervención terapéutica. Como parte de ello, enfatiza en la promoción de salud, diagnóstico temprano, tratamiento y rehabilitación de las afecciones comunes del quehacer deportivo. Conscientes de la importancia de la rehabilitación, ésta no está limitada a la atención de lesiones (o traumatología), sino que también a minimizar y/o eliminar aquellos factores de riesgo asociados con padecimientos frecuentes de nuestra población. Entre ellos, se identifican estilos de vida poco saludables tomando en consideración el más amplio contexto biológico, psicológico y social. Se elabora un plan de intervención dirigido a restablecer la armonía, el equilibrio y la convivencia entre el hombre y su ambiente.

Los recursos de SADCE están disponibles para aquellas instituciones nacionales o internacionales que comparten una filosofía común de trabajo en favor de la Salud Deportiva y las Ciencias del Ejercicio.

¿A qué personas están dirigidos los servicios de SADCE?

A cualquier persona o grupos de personas que tenga(n) interés en la actividad deportiva y en utilizar el ejercicio como un medio de promoción y mantenimiento de la salud. A esto le llamamos Salud Deportiva.

Entre algunos grupos previamente identificados como potenciales usuarios, se encuentra:

1. Aquellos ciudadanos de la comunidad puertorriqueña que deseen mejorar su calidad de vida con lo que ofrece SADCE.
2. Atletas de las Federaciones adscritas al Comité Olímpico de Puerto Rico.

3. Deportistas asociados a grupos cuya sede es el Albergue.
4. Estudiantes de la Escuela Superior del Albergue.
5. Miembros de instituciones públicas o privadas, académicas o no académicas.
6. Deportistas de países extranjeros.

¿Dónde está localizado el Centro de SADCE?

La ubicación de SADCE es en los terrenos del Albergue Olímpico, en Salinas, al sureste de la isla de Puerto Rico. Está inmediatamente al lado del puesto de peaje de la Autopista Las Américas. Basta con seguir las direcciones de los rótulos en la carretera para llegar hasta el Albergue. Una vez, aquí, pregunte por el complejo multideportivo-acuático y siga las flechas hasta la planta baja. Allí nos encontrará en la mejor disposición de ayudarlo.

¿Qué unidades componen a SADCE y qué servicios prestan?

Unidad de Servicios Primarios de Salud

En esta Unidad se establece el contacto inicial con el Programa de SADCE. Ofrece sus servicios de cuidado de salud en una forma personal, integral y coordinada. Lleva a cabo las siguientes actividades:

1. Promoción de salud: Orienta al usuario hacia la búsqueda de su estado óptimo funcional como persona estimulando la autoresponsabilidad por su salud.
2. Prevención en salud: Se refiere a las pruebas de cernimiento para la identificación temprana de condiciones que afectan la salud.
3. Evaluación y tratamiento: intervención correctiva para problemas, condiciones y/o enfermedades comunes que afectan a la población servida.

El ofrecimiento de estos servicios está fundamentado en el seguimiento continuo del estado de salud de la persona; por lo tanto, se estimula a que se utilicen independientemente de la identificación o surgimiento de un problema médico y/o enfermedad particular. Los miembros del equipo de profesionales de la salud que componen la unidad son: Médicos de Familia, Enfermera y Nutricionistas (Dietistas).

Unidad de Fisiología del Ejercicio

La fisiología del ejercicio es el estudio de las respuestas fisiológicas agudas al ejercicio y las adaptaciones al entrenamiento que sufre el cuerpo del ser humano. Todo atleta debe conocer sus fortalezas y debilidades funcionales y las modificaciones necesarias a ser efectuadas en un plan de entrenamiento para eliminar las deficiencias y

mantener o superar sus fortalezas. La Unidad de Fisiología del Ejercicio (UFE) puede proveer este tipo de información de varias maneras:

1. determinando el talento deportivo a temprana edad.
2. evaluando la condición fisiológica y los niveles de aptitud física utilizando pruebas específicas para un deporte.
3. identificando el grado de adaptación inducido por el ejercicio y el entrenamiento deportivo.
4. interpretando los resultados al entrenador y al atleta.
5. ofreciendo recomendaciones de programas de entrenamiento.

Las siguientes evaluaciones pueden ser efectuadas en la UFE:

Composición Corporal

Un exceso de grasa acumulada en el cuerpo puede impedir un rendimiento efectivo en varios deportes y como la masa muscular es responsable del movimiento, todo atleta necesita un bajo porcentaje de grasa y un alto porcentaje de masa magra (músculo, hueso, órganos). La UFE estima la composición corporal utilizando el procedimiento de pesaje bajo agua y mediante la antropometría. La composición corporal es el porcentaje del peso corporal que es grasa y masa magra. La determinación del porcentaje de grasa nos puede ayudar a determinar la cantidad de peso (grasa) que una persona puede perder sin afectar su estado de salud (rendimiento), o si un programa con pesas es necesario para ayudar a aumentar la masa muscular.

Bioquímica

La UFE cuenta con facilidades para análisis bioquímicos de parámetros relacionados con el rendimiento deportivo.

Función Neuromuscular

La fuerza, potencia y tolerancia local muscular son componentes importantes del rendimiento deportivo. Estas capacidades pueden ser evaluadas en forma específica para cada deporte. La cantidad de fuerza generada por el atleta durante un movimiento, el ángulo articular al cual la fuerza máxima es generada, el trabajo total efectuado la potencia (trabajo/tiempo) muscular y los efectos de la fatiga en estos parámetros también pueden ser evaluados. Las debilidades y fortalezas son identificadas y unas recomendaciones a la par son ofrecidas.

Pruebas Especiales

Pruebas de campo específicas para un deporte son utilizadas para evaluar la respuesta fisiológica durante la actividad deportiva en sí. Estas pruebas pueden ayudar al entrenador y al atleta a relacionar los resultados obtenidos en el laboratorio con la actividad efectuada durante la práctica y la competencia. Esta información nos ayuda a determinar los factores que deben ser enfatizados durante el entrenamiento.

Capacidad Aeróbica (noróbica)

La potencia aeróbica es la capacidad de transportar en la sangre y utilizar a nivel muscular el oxígeno del medio-ambiente para proveer la energía necesaria para la contracción muscular. Esta capacidad es muy importante para aquellos eventos que requieren tolerancia cardio-respiratoria (ej: maratón). la máxima capacidad aeróbica de un atleta puede ser evaluada a través de pruebas que asemejen la especialidad deportiva del mismo. Para eventos que requieren una menor duración del esfuerzo (ej: 100 metros) el atleta necesita producir una gran cantidad de energía a un ritmo acelerado. Esto ocasiona que el atleta utilice extensamente su sistema energético anaeróbico, lo que resulta en una acumulación de ácido láctico en el músculo y la sangre. Debido a que la presencia de una alta concentración de ácido láctico en el organismo está asociada con la fatiga, es importante evaluar la tolerancia del atleta a esta sustancia utilizando diferentes intensidades del ejercicio. Esto se efectúa mediante la toma de muestras de sangre. Como en toda evaluación fisiológica efectuada en la UFE, la determinación de los cambios inducidos por el entrenamiento en estas dos capacidades energéticas son de primordial importancia.

Unidad Biopsicosocial

La unidad biopsicosocial auna sus esfuerzos y trabaja de forma integrada a las demás unidades que componen el Centro para alcanzar los objetivos trazados.

El concepto biopsicosocial se refiere al modo en que visualizamos al ser humano como ente biológico, psíquico y social. Estos elementos forman una unidad; una totalidad indivisible. Es decir, el ser humano es visto como una entidad compleja, formada por diversos elementos, los cuales se encuentran en continua interacción y cambio.

Partimos de un enfoque heurístico, el cual asume que es necesario estudiar el conjunto del hombre y su ambiente como una totalidad que pierde su esencia si se desintegra. A este conjunto podemos llamarle sistema.

Los integrantes de esta Unidad entendemos que para alcanzar el desarrollo óptimo de las potencialidades humanas, es necesario considerar al ser humano en su contexto más amplio e integrado. Esto nos ayuda a entender los individuos, su familias y sus grupos. Partiendo de esta comprensión, elaboramos un plan de trabajo definido y ajustado a las necesidades específicas de los usuarios.

El grupo de trabajo está constituido por un médico-psiquiatra, una doctora en psicología deportiva, una psicóloga clínica y una trabajadora social. Las ciencias del comportamiento aplicadas a los atletas, deportistas y a los escenarios deportivos, investigan, como disciplinas científicas, aquellos procesos y fenómenos psíquicos y sociales que experimentamos los seres humanos antes, durante y después de la participación deportiva.

Esta unidad tiene disponible los siguientes servicios:

1. evaluación biopsicosocial de los deportistas y usuarios visitantes.

- a. entrevista inicial e historial personal y familiar.
- b. pruebas específicas para medir variables psicosociales y deportivas.
2. educación, consejería y orientación en el área de ciencias del comportamiento y psicología deportiva.
3. psicoterapia individual y/o grupal.
4. técnicas para el manejo adecuado del estrés, el dolor y la rehabilitación neuromuscular incluyendo biofeedback. ("biofeedback").
5. charlas educativas, talleres y conferencias.
6. programas de preparación psicológica que incluyen una o varias de las siguientes áreas:
 - a. técnicas de relajamiento
 - b. visualización e hipnosis
 - c. establecimiento de Metas
 - d. motivación
 - e. identificación de necesidades y/o recursos especiales.
 - f. simulación
 - g. técnicas de concentración - atención
 - h. técnicas de auto-control
 - i. reestructuración cognoscitiva
 - j. destrezas para mejorar comunicación
7. evaluación y seguimiento de aquellos deportistas con problemas de uso y abuso de sustancias prohibidas en la práctica del deporte.

Unidad de Salud Oral

Esta unidad promueve la salud oral, como parte de la salud general, por entender que ésta afecta la ejecución del individuo tanto en la actividad deportiva y/o el ejercicio como en los otros aspectos de su vida diaria.

Para lograr este objetivo los integrantes de la unidad, dentistas y asistentes dentales, enfatizan en las siguientes áreas:

Educación y prevención - se le provee al paciente información sobre los factores que precipitan enfermedades orales. Se educa sobre como prevenir las mismas con una dieta adecuada y control de placa dental mediante una buena técnica de cepillado y el uso regular del hilo dental.

Se fomenta el uso de protectores bucales especialmente en aquellos deportes de contacto. El uso de estos aparatos en deportes como boxeo, lucha, judo, baloncesto, etc... ayuda a evitar fractura de dientes, ruptura de labio o laceraciones que ocurren como consecuencias de trauma a la cavidad oral durante la práctica del deporte en particular. Se recomienda el uso de protectores ya que no sólo protegen las estructuras intraorales antes mencionadas sino que al ayudar a disminuir la severidad del golpe previenen otras complicaciones como fracturas, daño a la articulación temporomandibular etc...

Nuestra unidad provee los servicios de construcción de protectores bucales a aquellos atletas que practican deportes de contacto.

Evaluación - se hace un examen oral a cada paciente y se diagnostican aquellos problemas presentes. Se

establece un plan de tratamiento para aquellos que requieran intervención.

Tratamiento - se ofrece tratamiento para los problemas diagnosticados que requieren intervención primaria o secundaria. Aquellos que requieren intervención a nivel terciario se refieren a un especialista.

Seguimiento - se examina periódicamente a los pacientes para reevaluar su condición oral, la efectividad de las técnicas preventivas implementadas, reforzar la educación de ser necesario y dar tratamiento en caso de que se diagnostique algún problema nuevo.

Unidad de Asistencia Terapéutica

La unidad de Asistencia Terapéutica reúne un grupo de profesionales de la salud con entrenamiento especializado en la prevención, el diagnóstico, el tratamiento y la rehabilitación de lesiones atléticas. Los integrantes de esta unidad, especialistas en medicina física y rehabilitación (fisiatría), ortopedia y terapia física, en colaboración con la Unidad de Servicios Primarios de Salud, forman el equipo de trabajo de la Clínica de Traumatología Deportiva.

Esta unidad tiene disponible un servicio de terapia física que desarrolla actividades encaminadas a:

1. la evaluación de la integridad y el funcionamiento del sistema músculo-esquelético;
2. la aplicación de modalidades terapéuticas en el tratamiento y la rehabilitación de lesiones asociadas a la actividad deportiva y/o el ejercicio.
3. la prevención de dichas lesiones mediante la educación sobre el uso correcto de técnicas de entrenamiento.

Los planes para el desarrollo futuro de esta unidad incluyen especialistas en otras áreas de la medicina (por ej: cardiología, neumología) para la atención de problemas de salud que requieren una intervención diagnóstica y/o terapéutica especializada. El desarrollo de un servicio de estudios radiográficos y un laboratorio clínico para el análisis químico y hematológico (de sangre), nos permitirán, en un futuro cercano, ampliar los servicios diagnósticos en nuestro centro.

Unidad de Bioestadística y Computación

Esta unidad es la responsable del diseño e implementación del sistema de información computarizado sobre los diferentes servicios ofrecidos por el Centro; y de proporcionar la asesoría estadística correspondiente sobre la utilización de los datos generados por este sistema. Además, la unidad participa en la operacionalización de la metodología científica (investigación) a seguir en el Centro para el desarrollo de las Ciencias del Ejercicio; y de la creación de nuevos modelos estadísticos y epidemiológicos del campo de la Salud Deportiva.

Unidad de Recursos Educativos

Además de las unidades mencionadas anteriormente, nuestro centro está desarrollando una Unidad de Recursos Educativos. Dicha unidad consta de:

1. Sala de conferencias: Un amplio y cómodo salón donde se llevan a cabo actividades educativas (charlas, seminarios, talleres de estudio) y reuniones para el personal del Albergue y todo grupo de la comunidad interesado. La sala tiene recursos audiovisuales que facilitan, complementan y refuerzan el aprendizaje.
2. Sala de estudio: El SADCE está desarrollando una colección de revistas y libros relacionada con los aspectos técnicos y científicos del deporte para facilitar la educación, mejorar el servicio y estimular la investigación en las diversas áreas de la salud Deportiva y Ciencias y del Ejercicio.

¿Cómo establecer contacto con el Centro?

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¿Qué debe hacer para recibir los servicios del programa SADCE?

Trabajamos con un itinerario diario y semanal y atendemos los usuarios siguiendo un programa de citas.

Deberá indicarnos su interés particular y le haremos saber lo que podemos ofrecerle; dónde, cuándo y por quién.

Los servicios ¿conlleven costos? ¿Cómo puedo pagar?

Estos servicios tienen un costo módico que usted puede pagar en efectivo o mediante el uso de su plan Médico.

¿Por qué trabajamos en SADCE?

En el Centro SADCE se promueve la actividad deportiva y el ejercicio porque entendemos que cuidan, ocupan, educan, producen y garantizan las funciones de una cultura sana, una cultura que fortalezca el quehacer moral. Hacemos nuestro trabajo con amor y conscientes de que la actividad deportiva nos acerca a cumplir cabalmente con nuestras responsabilidades individuales y colectivas para elevar la meta de nuestra trascendencia humana. La nuestra, es una brega por la solidaridad y la dignidad de nuestro pueblo.

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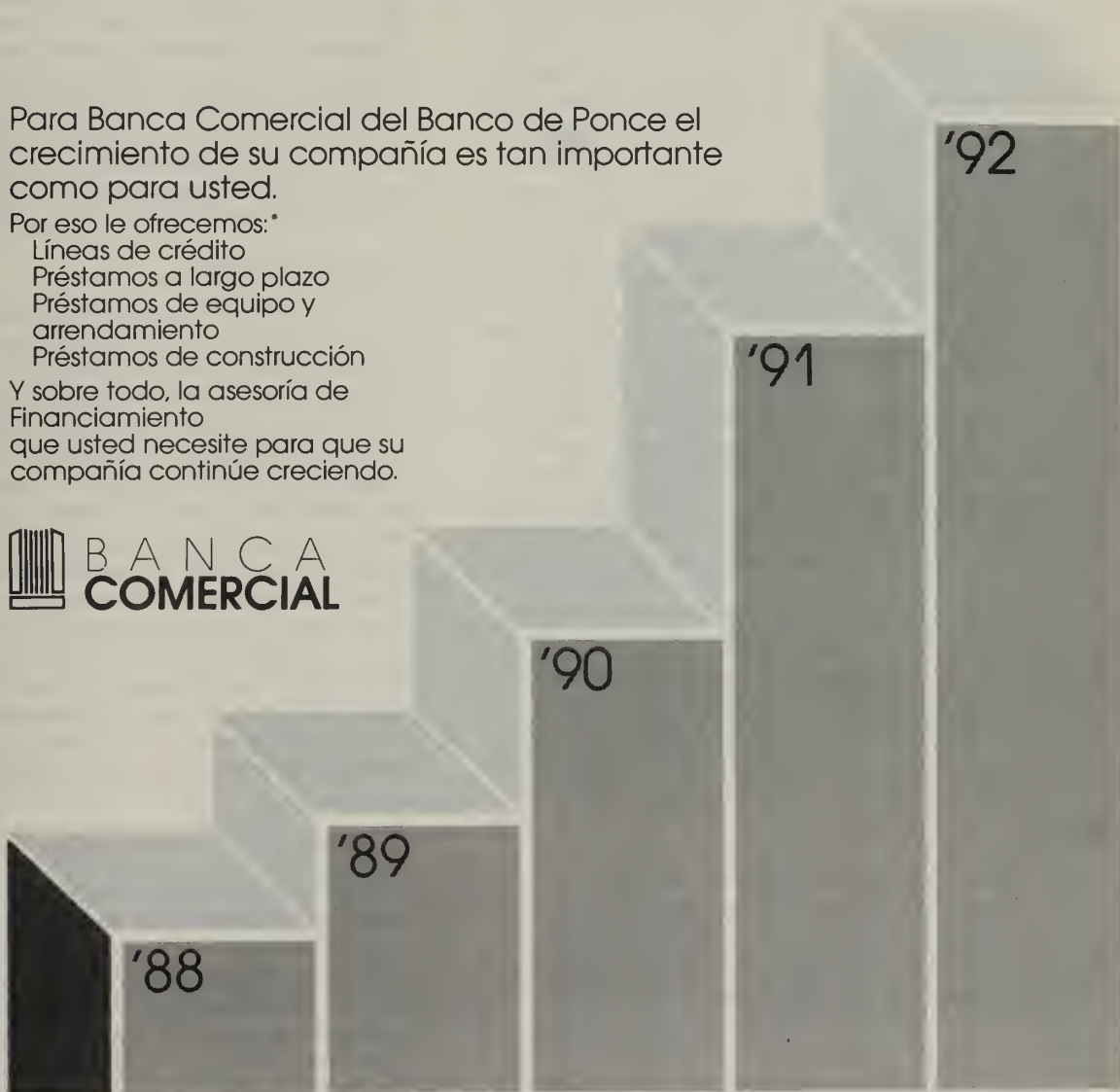
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Eye Injuries and Eye Protection in Sports: A Position Statement from the International Federation of Sports Medicine*

The International Federation of Sports Medicine calls attention to the fact that, while eye injuries in sports can be relatively frequent, they are almost completely preventable. Loss of sight, even in one eye, involves changes in lifestyle for the individual and serious financial and social consequences both for the individual and for society as a whole. It is imperative that sport eye injury risk be reduced to as low a level as possible by enforcement of existing safety rules or by rules changes, where applicable. All athletes should be prescribed eye protectors where appropriate to the sport.

Sports can be classified on the basis of low risk, high risk, and extremely high risk for eye injury. Most sports that pose risk for unprotected eyes can be made quite safe with the use of appropriate protective devices. Eye examination and counseling should play an important part in the screening physical examination for every athlete prior to sports participation. The athlete deserves a careful explanation of the risk of eye injury, both with and without various types of eye protectors in the proposed sport. Athletes who are functionally one-eyed must have their status diagnosed and appropriate eye protection prescribed.

Glass lenses, ordinary plastic lenses, and open (lenseless) eyeguards do *not* provide adequate protection for those involved in active sports. In many situations, their use can increase the risk for and the severity of eye injury. As contact lenses do not protect the athlete from serious eye injury, they should only be worn in combination with recommended sport eye protectors.

Eye Injury Risk in Sports

Eye injury risk is almost totally related to the particular type of sport.^{10, 11, 13} Low risk sports do not involve a thrown or hit ball, a bat or a stick, or close aggressive play with body contact. Examples include track and field, swimming, gymnastics, and rowing.

Sports with high risk of eye injury (when protective devices are not being worn) involve a high speed ball (or puck), the use of a bat or stick, close aggressive play with intentional or unintentional body contact and collision, or a combination of these factors. Examples include hockey (ice, field, and street), the racket sports (racquetball, squash, tennis, badminton), lacrosse (men's

and women's), handball, baseball, basketball, football (U.S., Canadian, Australian), soccer, and volleyball.^{3, 9, 11, 14} The incidence of serious eye injury in these sports is a source of great concern, but adequate eye protective devices are available.^{1, 2, 4, 5, 8}

Sports involving extremely high risk for eye injury are the combative sports such as boxing and full-contact karate^{7, 11, 12} for which effective eye protective devices are not available. The functionally one-eyed athlete should be strongly advised against participation in such sports.

Other Risks Factors

It is suspected but not yet proven that risk for eye injury may also be related to physical development, skill level, and existing visual impairment. It is believed that a beginner is more prone to injuries that are intermediate or advanced players because beginners have not yet learned or refined the necessary skills to master the sport. However, in such sports as hockey, squash, and racquetball, highly skilled athletes play a faster game with more aggressiveness and, thus, may be subject to a higher eye injury risk than other participants.

Any eye condition that could be made worse if the eye were to be struck places the athlete at increased risk of serious eye injury. Athletes with retinal degenerations, thin sclera, prior eye surgery (including cataract surgery, retinal detachment surgery, and radial keratotomy), prior serious eye injury, or eye disease should seek consultation with an ophthalmologist before participating in a sport.

The Functionally One-Eyed Athlete

Sports participants with only one good eye are at particular risk since a serious injury to the good eye could leave the person with a severe visual handicap or permanently blind. Any person with good vision in only one eye should consult with an ophthalmologist on whether to participate, then the person should wear maximum protection for the particular sport for all practice sessions and for competition.

A person is functionally one-eyed when loss of the better eye would result in a significant change in lifestyle due to poorer vision in the remaining eye. There is no question that a person with 6/60 (20/200) or poorer best-corrected vision in one eye is functionally one-eyed since loss of the good eye would result in legal or total blindness, with its attendant burden both to the individual and society. On the other hand, ophthalmologists believe that most persons with one eye function quite well with 6/12 (20/40) or better vision in that eye.

Every athlete who tests less than 6/12 (20/40) with glasses, if worn, on the screening examination should be

*This position statement was prepared by Paul F. Vinger, M.D., (Lexington, MA, USA) and Howard G. Knuttgen, Ph.D. (Boston, MA, USA) in collaboration with Michael Easterbrook, M.D. (Toronto, Ont, Canada), Thomas J. Pashby, M.D. (Don Mills, Ont, Canada), and Dieter Schnell, M.D. (Waldbröl, Federal Republic of Germany). Reprinted with permission.

evaluated by an optometrist or an ophthalmologist to determine if the subnormal vision is simply due to a change in refraction. If the best-corrected vision in either eye is less than 6/12 (20/40) after refraction, ophthalmological evaluation to obtain a definitive diagnosis of the visual deficit is indicated. If the athlete is functionally one-eyed, the potential serious, long-term consequences of injury to the better eye should be discussed in detail.

Eye Protectors

Most eye (and face) injuries could be prevented or, at least, the effects of such injuries minimized by using protective eyewear. Normal "streetwear" eyeglass frames with 2 mm polycarbonate lenses give adequate, cosmetically acceptable protection for routine use by active people. Such protective glasses are recommended for daily wear by the visually impaired or functionally one-eyed athlete. They are also satisfactory for athletes in competition who wear eyeglasses and participate in low risk sports.

Molded polycarbonate frames and lenses (plano/non-prescription protective eyewear) are suggested for contact lens wearers and athletes who ordinarily do not wear glasses but participate in moderate to high-risk, non contact sports (eg., racket sports, baseball, basketball). In high risk contact or collision sports, they can be used in combination with a face mask or helmet with face protection for additional protection. Such protective glasses are recommended to the functionally one-eyed athlete who does not require prescription protective eyewear in the good eye to be used in combination with a face mask and helmet for higher risk contact sports. Face masks or helmets with face protection are required for use in the high risk contact or collision sports (e.g., ice hockey, U.S. football). The face mask may consist of metal wire, coated wire, or a transparent polycarbonate shield.

When protective eyewear has been employed in racket sports and face protection devices employed in hockey, eye injuries have been eliminated.^{6, 8}

Routine Examination

General practitioners providing medical screening for athletes should have facilities for vision testing and basic eye examination at their disposal and be aware of both the basic principles of eye protection in sports and the available protective eyewear. It is recommended that athletes have their vision tested and eyes examined on a regular basis. Vision or eye problems are best corrected by an eye care specialist when detected early. An examination also offers an opportunity to discuss any sports vision needs and the most appropriate type of protective eyewear.

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Appendix

Eye and Face Protector Standards

Racket sports (sports frame and plano sports eyeguards):

- ATSM 7803-88 Eye protection for use by players of racket sports
- CSA P400-M 1982 Racket sports eye protection, preliminary standard

Hockey:

- ASTM F513-86 Consumer safety specification for eye and face protective equipment for hockey players
- CSA CAN 3-Z262.2-M83 Face protectors for ice hockey and box lacrosse players

Baseball:

- ASTM F910 Qualifications for faceguards for youth baseball

Skiing:

- ASTM F659 Specifications for eye protective devices for alpine skiing

ASTM - American Society for Testing and Materials
CSA - Canadian Standards Association

Sudden Cardiac Death During Exercise: Incidence, Aetiology and Prevention*

U. Brüggmann, MD**

R. Hopf, MD**

M. Kaltenbach, MD**

Sudden cardiac death (SCD) is unexpected natural death occurring in the midst of complete well-being or in a phase of stability and/or improvement of a chronic disease. It is mainly caused by ventricular fibrillation (70-90%) or asystolia. With regard to the interval between the onset of symptoms and cessation of life, the designation "sudden cardiac death" has been employed without consensus. In some reports it has been stated that this interval lasted up to 24 hours, whereas in more recent studies a limit of one hour has been established.

The aim of this article is to give an overview of the incidence of SCD during physical activity and to discuss the reasons for death and the possibilities of prevention.

Incidence of sudden cardiac death

a) In the whole population

SCD represents a major medical and socio-economic problem in the Western world. According to mortality statistics, cardiovascular diseases still account for most deaths, and roughly three fourths of these deaths occur suddenly; 30% of all deaths in the age group of 40 to 60 years are therefore defined as sudden cardiac death. The famous Framingham Study has shown that the rate of SCD was 3/10,000, 10/10,000 and 27/10,000 in men aged 35-44, 45-54 and 55-64 years respectively.

b) During sports activities

In 1979, Koplan reported on more than 4 million U.S. long-distance runners aged 20-59 years who exercised at least one hour per week. From normal statistics, without taking any intervention whatsoever into consideration, one would expect a death rate of 10/10,000 persons in this age group. However, this study only revealed a rate of 3/10,000 during the "active running period". The authors therefore assumed that running is considerably less dangerous than other less vigorous everyday exercises.

Moritz and Zamchek have shown that only 15% of 98 fatalities with organic lesions occurred during sleep and 29% during vigorous activity. On the other hand, no connection between activity and occurrence of death was found in 127 autopsies without organic lesions. Similar results have been reported by Vuori who found a close correlation between the interval of symptom onset with subsequent death and the extent of physical activity in

2,606 cardiac fatalities recorded in one year in Finland. The hypothesis that physical activity can lead to a higher incidence of SCD, at least in the case of a predamaged heart, is strengthened by the fact that the majority of cases examined revealed organopathological changes-primarily in the cardiovascular system.

Aetiology of sudden cardiac death

Between 1966 and 1975, Munschek analysed 124 deaths connected with sports activities and established a primary cardiac cause of death in 67 subjects, of which 59 had been suffering from coronary artery disease (CAD). Many other statistics and case reports have shown pre-existing cardiac disease that had been unknown before death occurred. Jokl stated in 1971 that in no case in which death occurred during physical activity did autopsy show an absence of severe illness.

Hypertrophic cardiomyopathy (HCM) is another important cause, especially in young training cohorts. Maron described 11 sudden deaths in children with HCM of whom 3 had been completely and 6 nearly asymptomatic. He also reported on 26 patients whose sudden cardiac deaths were the first manifestation of HCM. Contrary to earlier reports in the literature, myocarditis has in only a few cases led to SCD during sports activities. Other cardiac diseases such as congenital shunts, acquired valve lesions, tumours, viral infections, ruptured aortic aneurysms, and other forms of cardiomyopathies or electrophysiological abnormalities such as WPW syndrome or QT-prolongation rarely cause fatal events.

Patients at risk

From long-term studies we know that patients with CAD and impaired left ventricular function, malignant arrhythmias and variant angina as well as those who smoke or have high blood pressure are at increased risk (Table 1). To prevent SCD or other undesired cardiac events during exercise, we should consider other contraindications (Table 2).

Everyone who exercises should undergo minimal examination to exclude haemodynamically significant cardiac disease. This examination should include the individual's history, physical examination, ECG at rest and during exercise, chest X-ray, some laboratory parameters and, if possible, echocardiography. Hollmann has pointed out that two-thirds of all SCD can be prevented by such examination.

The risk from ergometry itself is very low. Kaltenbach and co-workers have documented in a sample statistic that only 18 deaths occurred during 1.7 million ergometries.

*Reprinted from *Heart Beat, Journal of the International Society and Federation of Cardiology*, March 1988, p 5-6

**From the University of Frankfurt, Department of Cardiology, Frankfurt, FRG

Table 1

Patients at risk

1. CAD with unstable angina
2. Decreased LV-function (EF < 30%)
3. High-grade arrhythmias
4. Connatal or acquired heart defects
5. Cardiomyopathies
6. Cor pulmonale
7. Arterial hypertension
8. Acute infections
9. Endocrine disturbances
10. Electrolyte disturbances
11. Decreased aerobic capacity
12. Smoking

Table 2

Contraindications, Especially for Older Patients or Patients at Risk (modified from Hollmann)

1. High temperatures combined with high air humidity
2. Very low temperatures
3. Atmospheric pressure changes
4. Unadapted to altitude
5. Exercising after a big meal
6. Exercising after long-term immobility

Primary prevention

Whether regular exercise can reduce the number of SCDs, in the sense of primary prevention, cannot be answered conclusively on the basis of the current literature. The respective studies have methodological deficiencies, primarily because the self-selection of patients has been neglected and because these studies have been retrospectively conceived.

An example is given in the extensive epidemiological publications by Pfaffenberger in which a positive influence from increased physical activity on the rate of manifest coronary heart diseases was established. The question of selection, however, remains unanswered: Are healthy people more active or are active people more healthy?

In 1984, Siscovick analysed 133 cases of SCD without previously known heart disease. Among the group with overall low stress levels, the risk of cardiac arrest during vigorous short-term physical exercise was 56 times higher than at rest. With overall high stress levels the risk was only 5 times higher. The total risk of SCD in the group of patients exercising more intensively and frequently was, however, only 40% compared with the less active group. It may thus be concluded that the risk of SCD during strenuous intensive exercise is slightly increased whereas frequent high-stress exercise is more likely to reduce the overall risk.

In a series of animal experiments, a reduction in ventricular fibrillation in coronary artery occlusions was documented after training dogs over a period of six weeks. Thus, regular physical activity may possibly reduce the threshold of myocardial fibrillation in man.

Secondary prevention

There are only a few well-designed prospective studies concerning secondary prevention. In the National Exercise and Heart Disease Project, the effects of a fixed exercise programme in 651 post infarction patients were analysed. The cumulative 3-year mortality was 7.3% for the control group and 4.6% for the training group. Although this difference was not significant it showed no deleterious effects. A 1-hour training period 3 times a week did not increase the SCD rate of the infarction patients. No substantial influence on mortality of the reinfarction rate was found in the Ontario Exercise Heart Collaborative Study and in the Wilhelmson Study. On the showing of all secondary prevention studies, the results are not impressive.

Conclusion

The results make it very difficult to define the role of physical activity with regard to the triggering of SCD on the one hand and its prevention on the other hand. Sports can prevent damage to health but can also provoke acute risks for the cardiovascular system — especially if contraindications are disregarded and if risk patients are not identified. The incidence rate of undesired effects can be substantially lowered by means of simple preliminary examinations and in particular by careful history taking. Thus more benefits than risks would be gained from sports activities.

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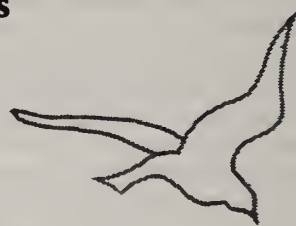
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Case Presentation

Congenital Esophageal Stenosis: A Case Presentation

Manuel R. Prats, MD
Idelisa Lleras, MD
Heriberto Pagán Saez, MD

Congenital esophageal stenosis is the least common of the anomalies involving the esophagus and the tracheobronchial tree.¹ When present, its most common localizations is at the junction of the middle and distal thirds of the esophagus.

The case to be presented is to the best of our knowledge one of the youngest patient diagnosed with such malformation.

Case Report

A one day old female newborn was transferred to the University Pediatric Hospital for management of an imperforate anus. The physical examination confirmed the presence of imperforate anus and a rectovaginal fistula. As part of her pre-operative workup, supine anteroposterior and lateral chest X-rays were obtained. The lateral projection showed an air column interposed between the trachea and a nasogastric tube with its tip at the gastric fundus. (Figure 1)

Because of this finding, a posterior transmural esophageal perforation was suspected. A barium contrast study was done using a nasogastric tube with its tip placed at the thoracic inlet. It revealed a markedly dilated proximal esophageal pouch with a long segmental area of stenosis (2 cm.) at the junction of the middle and distal thirds of the esophagus. (Figures 2 a, b)

Delayed passage of contrast material into the stomach was noted. The stenotic segment was aperistaltic and reversed peristaltic waves were seen proximally to the stenosis. A barium contrast esophagogram done 6 days later revealed the same findings.

The patient was taken to the operating room two days after the second study for an esophagoscopy that revealed no evidence of esophagitis or tear at the posterior aspect of the pharynx. A congenital esophageal stenosis was suspected, dilatation was attempted without success and a Stamm gastrostomy was performed. The



Figure 1. Lateral supine chest x ray demonstrating an air column interposed between the trachea and a nasogastric tube running posteriorly in a prevertebral location.

patient improved and twelve days later a retrograde dilatation per gastrostomy was performed using a French filiform catheter up to a 14 French dilator. A follow up esophagogram performed 6 days after a second dilatation revealed distention of the stenotic segment with adequate passage of contrast material into the stomach.

The patient was started on oral feedings with excellent toleration so the gastrostomy was closed and the patient discharged from the hospital.



Figure 2 a-b. Barium contrast esophagogram demonstrating an area of stenosis at the junction of the mid and distal third of the esophagus in both AP and lateral projections.



Figure 3. Repeated barium study showing same findings as in figure 2.



Figure 4 a-b. Follow up esophagogram on AP and oblique projections after several dilatations showing adequate distention of stenotic segment.



Figure 4-b

Discussion

Congenital esophageal stenosis is a rare entity, although it appears to be more frequent than previous literature reports indicate.¹ It occurs most commonly at the junction of the middle and distal thirds of the esophagus and its true incidence is estimated to be 1 per 25,000 live births.

The exact cause of congenital esophageal stenosis is not known, although failure of the epithelial vacuoles to coalesce has been implicated in the past.² This condition may be associated with other anomalies of the tracheobronchial tree such as tracheoesophageal fistula and esophageal atresia. This strongly suggests that congenital esophageal stenosis is but another manifestation of lesions associated with abnormal differentiation of the respiratory tract arising from the foregut.

Congenital esophageal narrowing can occur independently or in association with webs. There are three types of lesions that may be identified roentgenographically as areas of stenosis; an independently occurring esophageal web, an area of segmental stenosis or an esophageal web occurring in association with an area of segmental stenosis. A study of the embryology involved suggests that both webs and areas of segmental stenosis are different manifestations of the same developmental process.

A dilated esophagus proximal to the stenosis and reverse peristaltic activity originating at the level of the stenosis are the radiographic findings seen in congenital esophageal stenosis. The areas of segmental stenosis are usually 0.5 to 1.5 cm. long and in order to establish the congenital nature of the stenosis, a normal gastroesophageal junction with no gastroesophageal reflux or hiatal hernia is essential. In our case all these criteria are fulfilled. Previous reports have stated that neonatal pharyngoesophageal perforation can simulate esophageal atresia. Initially the discussed esophageal stenosis was interpreted as posterior esophageal transmural perforation, but this perforation most commonly occurs after multiple intubations on a pre-term or small for gestational age newborn.

Most cases of esophageal stenosis can be adequately managed by esophagoscopy and sequential dilatations of the narrowed segment. In our patient adequate passage of contrast material was obtained after two separate dilatations.

This case can be considered as one of the youngest patients with congenital esophageal stenosis diagnosed. Symptoms usually appear at three to four months of age when solid foods are added to the diet and is manifested clinically with recurrent vomiting. In the reported case a definitive diagnosis was made at 8 days of age.

Resumen: La estenosis congénita del esófago ocurre más frecuentemente en la unión del esófago medio y el distal. Es la menos común de las anomalías que afectan el esófago y el árbol traqueobronquial.

Reportamos un caso con dicha anomalía que se interpretó inicialmente como una perforación transmural posterior del esófago en un recién nacido. Este es uno de los pacientes más jóvenes donde se ha hecho el diagnóstico.

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Echocardiography Diagnosis of A Persistent Left Superior Vena Cava Draining Into the Coronary Sinus

Charles D. Johnson, MD, FACC

Echocardiography has assumed in recent years a major diagnostic role in cardiology, enabling the noninvasive diagnosis of sundry congenital and acquired heart lesions.¹ The following cases and review intend to demonstrate its value as a rapid and easy, noninvasive diagnostic method for persistent left superior vena cava (PLSVC) draining into the coronary sinus (CS).

Summary: This communication, of brief case reports and literature review, addresses the echocardiographic diagnosis of a persistent left superior vena cava draining into the coronary sinus. The association of a persistent left superior vena cava with a large coronary sinus by echocardiography, and with other cardiac defects, is emphasized.

Case 1. This 29-year-old female suffered from dyspnea, palpitations and fatigability. A grade 4/6 systolic

murmur was heard at the left sternal border and there was fixed splitting of S₂. The electrocardiogram (ECG) showed right bundle branch block. The chest x-ray showed slight cardiomegaly and prominence of pulmonary blood flow. Her M-mode and two-dimensional (2-D) echocardiograms are illustrated in Figures 1 A-1D.

Case 2. This young male drug addict with suspected endocarditis, had no other pertinent findings. His echocardiograms are illustrated in Figures 2A and 2B.

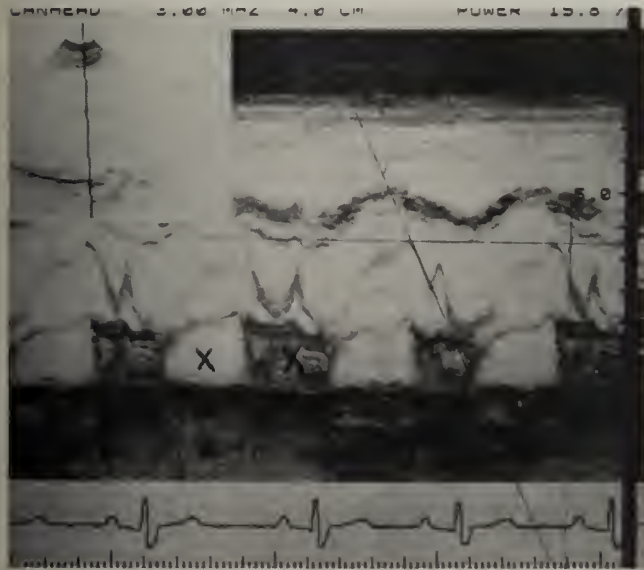


Figure 1-A. M-mode echocardiogram. The checkerboard light and dark rectangular areas behind the mitral valve (MV) represent the dilated coronary sinus (CS), marked X. The electrocardiogram (ECG) is at the bottom of the tracing.

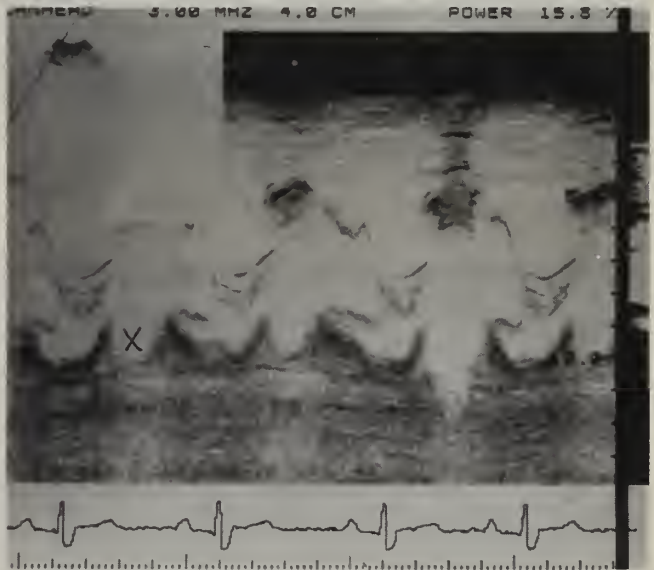


Figure 1-B. Shows only remnants of the CS (X).

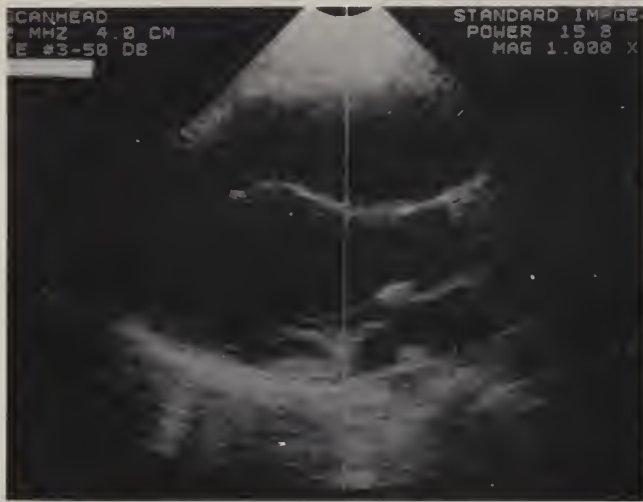


Figure 1-C. Parasternal long-axis view (PSLAX). The circular clear structure (X) represents the CS. Two-dimensional echocardiogram.



Figure 1-D. Similar to Figure 1-C

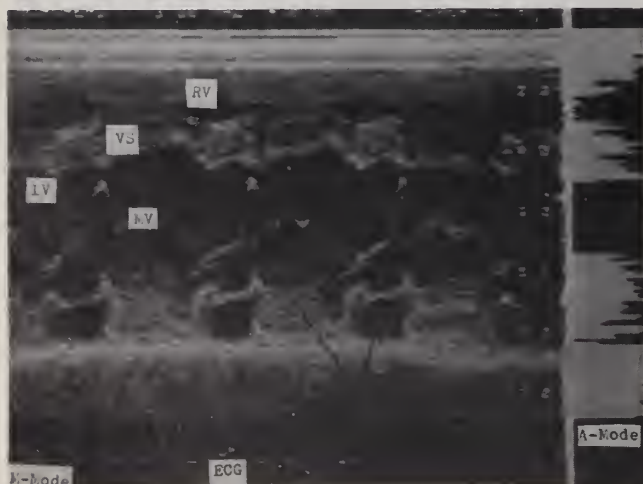


Figure 2-A. M-mode echocardiogram. The arrowed structures reflect the dilated CS. RV-right ventricle. VS-ventricular septum. LV-left ventricle.

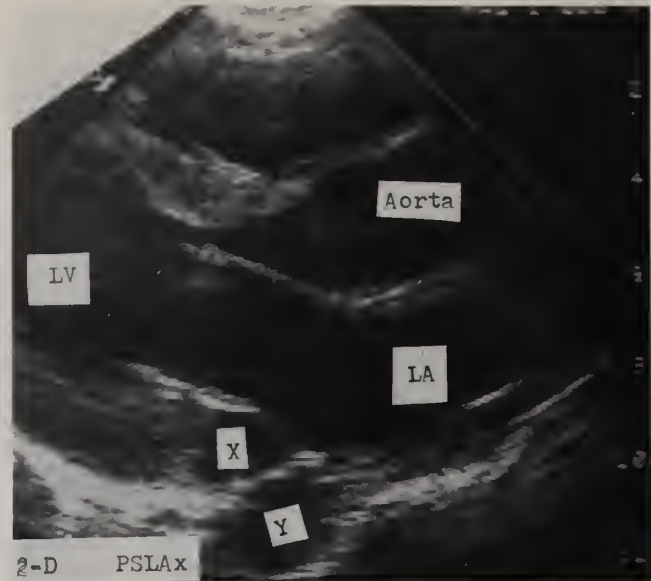


Figure 2-B. Two-dimensional echocardiogram. X marks the dilated CS.

Results

Cardiac catheterization in Case 1, revealed a large atrial septal defect (ASD). At open heart surgery a large secundum ASD and PLSVC were found.

Echocardiograms showed a dilated CS and PLSVC. In Figures 1A and 2A, note the checkerboard light and dark rectangular areas behind the mitral valve (MV), which is the dilated CS as seen on M-mode echocardiography. There is a curvilinear, dense echo just behind the posterior leaflet of the MV (formed from the contiguous wall of the left atrium (LA) and the anterior wall of the CS, and another such echo forms the posterior wall of the CS. Figure 1 B showed only remnants of the CS.

Figures 1C, 1D and 2B, are 2-D parasternal long axis (PSLAX) views. Note the circular clear structure at the posterior atrioventricular (AV) groove level (junction of the LA and posterior leaflet of the MV, denoted X in the figures), which represents the dilated CS. Injection of agitated saline in the left arm of case 1 produced opacification of this structure, confirming the diagnosis. A right arm injection showed a small right-to-left shunt at the atrial level. Y in Figure 2B is probably the descending aorta.

Discussion

A PLSVC connecting to the CS is relatively common and exists in 0.3 - 0.5% of the general population, and in 3-10% of patients with congenital heart disease. Ten to 17% of these have no right superior vena cava.²⁻⁷ A PLSVC as an isolated finding is rare and has little clinical significance in itself.^{1, 3, 7} However, a PLSVC may be associated with cardiac electrical instability, supraventricular and ventricular tachycardias, a CS rhythm, T wave changes, abnormalities of AV conduction and a congenital preexcitation pattern,⁷⁻¹⁰ and it may introduce technical implications for cardiac catheterization, transvenous pacemaker implantation and cardiac surgery.^{2, 3, 5, 6} In 7-10% of cases the PLSVC may

terminate in the LA.³ Moreover, a PLSVC may reflect and be associated with a variety of congenital heart defects.^{4, 7, 11} Table I

Table I

Defects Associated with A Persistent Left Superior Vena Cava

Atrial and. Ventricular septal defects.
Tetralogy of Fallot.
Single ventricle.
Coarctation of aorta.
Absence of right superior vena cava.
Total anomalous pulmonary venous connection to coronary sinus.
Right-to-left shunts, etc.
Any defect producing augmented coronary sinus blood flow.
Tricuspid insufficiency. Congestive heart failure.
Malpositions of the heart.

A dilated CS by echocardiography may reflect a PLSVC since the latter usually drains into the CS and then into the right atrium (RA). On M-mode echocardiography a distinct linear, dense echo is present either within the LA or behind the MV leaflet, which represents the combined, contiguous posterior wall of the LA and the anterior wall of the CS. This dense echo shows a diastolic, or systolic, anterior motion and may simulate that of the anterior mitral leaflet. The clear space behind the dense line is the CS. A 2-D PSLAx echocardiogram typically presents a dilated circular or oval structure within the posterior AV groove between the LA and left ventricle (LV) near the posterior leaflet of the MV, which is frequently pulsatile as a collapsible common wall with the LA. On an apical 4-chamber (Ap4C) view it is seen along the lateral border of the LA. Parasternal short axis (PSShAx) views show the echo-free, crescent-shaped CS posterior and medial to the LV (MV) and LA junction, moving with the AV groove, and opening into the RA. The PLSVC is sometimes visualized as a dilated vertical vein entering the CS.^{1, 4, 6, 7, 11-18}

Contrast confirms the nature of the anomaly. Saline contrast injected into a left arm vein fills first the CS with microbubble echoes, and subsequently the RA and right ventricle (RV) fill via the CS. A right arm injection shows only microbubbles within the RA and RV.^{4, 5, 7, 11, 13, 17-19}

Recently, Doppler echocardiography, from the subcostal and suprasternal notch views, has shown increased flow velocities at the entrances of the CS to the RA, and negative continuous low amplitude, biphasic velocities within the PLSVC that could be mapped to the level of the CS.¹⁸

Differential diagnosis of a dilated CS and PLSVC

Table II

Differential Diagnosis of A Dilated Coronary Sinus and Persistent Left Superior Vena Cava

The persistent left superior vena cava itself. (If isolated, the right and left superior vena cava and the right ventricle are normal in size).
The normal posterior leaflet of the mitral valve, pulmonary veins, the descending aorta and the left atrial appendage.
Cor triatriatum. Supravalvular mitral ring.
Left atrial myxoma or thrombus
Pericardial effusion or cyst
Mitral stenosis. Thickened chordae tendineae. Mitral valve prolapse.
Total anomalous pulmonary venous connection to the coronary sinus.

comprise several conditions^{4, 7, 13} as listed in Table II.

Although clinical observation for a dominant A wave in the left internal jugular vein, and a chest x-ray without or with contrast media injection, have been useful, 2-D and Doppler echocardiography may be the most simple, rapid and prudent method for the diagnosis of a PLSVC draining into the CS.^{7, 17, 18}

Resumen: Este manuscrito de reportes de casos breves y repaso de literatura, trata sobre el diagnóstico ecocardiográfico de un drenaje persistente de la vena cava superior izquierda al seno coronario. Se enfatiza la asociación entre el drenaje persistente de la vena cava superior izquierda y el seno coronario por ecocardiografía, además de con otros defectos cardíacos.

Acknowledgement

The echocardiograms were performed in the NonInvasive Laboratory of the University Hospital.

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**San Pablo Medical Center and
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*** 12th Anniversary Scientific Program ***

Seminar in Cardiology, Cardiovascular Surgery and Intensive Care Medicine

October 28, 29 and 30, 1988

San Pablo Hospital Amphitheater

Friday, October 28 (PM)

7:00	Registration and Welcome Cocktail	
8:00	Introduction	Dr. Rafael Brito
8:15	Muscle Physiology and Rehabilitation: Cardiovascular Response to Exercise	Dr. Walter Frontera
8:45	Pathogenesis of Arteriosclerosis	Dr. Ramzy S. Cotran
9:30	Cardiovascular Surgery Historical Review	Dr. Ernest Traad

Saturday, October 29 (AM)

Moderator: Dr. Rafael Brito

8:00	Registration Coffee and Pastries	
9:00	Thromboembolic Agents: Management and Risks	Dr. Juan M. Igartúa
9:20	Controversies in the Management of Acute Myocardial Infarction	Dr. George García Gregory
9:40	Reoperative Cardiac Surgery: Indications and Expected Results	Dr. Ernest Traad
10:00	Surgical Management of Tachyarrhythmia	Dr. Isaac Gielshinsky
10:30	Break	
10:45	Frontiers in Cardiovascular Anesthesia	Dr. Marcos Zuazo
11:05	PTCA vs Coronary Artery Disease Surgery	Dr. Isaac Gielshinsky
11:35	Surgical Management of Complications in Acute Myocardial Infarction	Dr. Manuel Martínez
11:55	Mitral Valve Repair Surgery	Dr. David Cohen
12:30	Questions and Answers	
12:45	Lunch	

Saturday, October 29 (PM)

Moderator: Dr. Manuel Lores

1:45	Heart Transplantation	Dr. David Cohen
2:15	Transfusion Requirement in Cardiac Surgery	Dr. John D. Milam
2:45	Post Operative Management in Cardiac Surgery	Dr. James T. Gallagher
3:15	Break	
3:30	Integrity of Conduction System After Heart Transplantation	Dr. J. Villafañe, Jr.
3:50	Lung Physiology and Ultra High Frequency Ventilation	Dr. James T. Gallagher
4:20	Complications in the Critical Care Unit	Dr. Víctor Salcedo
4:50	Intraoperative Blood Salvage	Dr. John D. Milam
5:20	Pharmacologic Therapy During Mechanical Ventilation	Dr. James T. Gallagher
5:40	Questions and Answers	

Sunday, October 30 (AM)

Moderator: Dr. G. García-Gregory

8:00	Registration Coffee and Pastries	
9:00	Rheumatic Heart Disease Revisited	Dr. Arturo Medina Ruiz
9:20	Kawasaki Disease Cardiovascular Complications	Dr. Rafael Villavicencio
9:50	Interventional Cardiac Catheterization in Children	Dr. J. Villafañe, Jr.
10:20	Surgical Management of Cardiac Arrhythmias in Children	Dr. Fred Crawford
10:50	Break	
11:00	Pathological Considerations in Endomyocardial Biopsies	Dr. I. Cohen
11:30	Cardiovascular Applications Laser Angioplasty	Dr. Christopher White

Sunday, October 30 (PM)

12:00	Frontiers of Shock, Pharmacology and Metabolism	Dr. Marcos Zuazo
12:30	Current Devices in Cardiac Prosthesis	Dr. Fred Crawford
1:00	Questions and Answers	
1:15	Anniversary Lunch	

GUEST SPEAKERS

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San Pablo Medical Center

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Zuazo, Marcos (MD)
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Baylor College of Medicine
Houston, Texas

Is Aminophylline Useful in Chronic Obstructive Pulmonary Disease? When Should Corticosteroids be Used?

Ramón Figueroa Lebrón, MD, FACP

In the treatment of chronic obstructive pulmonary disease (COPD) with exacerbation the literature has included in the last six month studies challenging the benefits of intravenous (IV) aminophylline when compared to placebo. The parameters used to evaluate improvements were FVC, FEV₁, arterial blood gases and verbal dyspnea index. If one reads these studies with an "open mind", something that is quite difficult to achieve by a physician who has relied on xanthines for over 25 years this question immediately arises: Is aminophylline really effective?

The action of IV xanthine in reversible airway obstruction is proven, but it appears that steroids and inhaled beta agonists are better in patients with COPD. Up to these studies we learned and taught that IV xanthines were the first line therapy in patients with bronchospasm without making a distinction between "reversible" and "nonreversible" airways obstruction. From now on we should make that distinction before submitting patients to the gastric but sometimes more serious side effects of xanthines. How can we make such a distinction in a rapid, accurate and inexpensive fashion?

We have to accept the fact that nowadays we have diagnostic tests for airway obstruction more reliable than the intelligent use of the stethoscope. That peak expiratory flow (PEF), FEV₁ and flow volume loop can be used in the office and emergency room settings for the physician to choose the most adequate management regimen for a given patient with respiratory distress. These tests of airway obstruction can be very reproducible; very easy to perform; they are inexpensive and provide the physician and the patient more security in the decision between in or out patient management and between xanthines or beta agonists plus steroids. The observations are there for everyone to evaluate including the third party payors.

The documented effectiveness or ineffectiveness of IV xanthines in the emergency room should help us look at the early use of corticosteroids with more assurance, without the tint of shame that we have felt along the years when we have had to use them in patients with bronchospasm.

Steroids are indicated in severe acute asthma or status asthmaticus. Under these conditions they can prevent

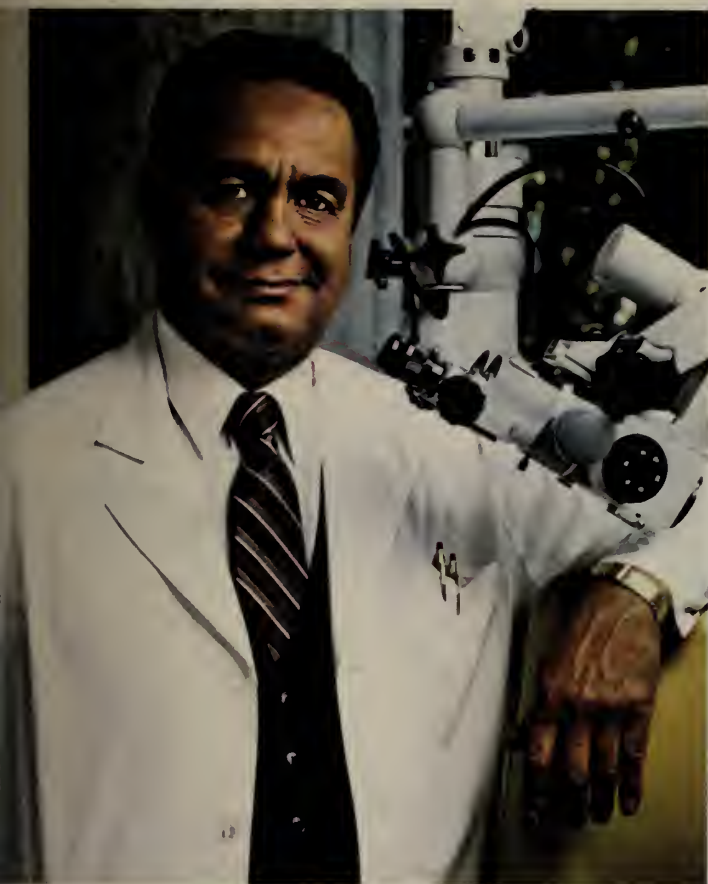
sudden death and reduce the incidence of subsequent relapses of asthma. If the dose is tapered within a few weeks, adrenal suppression and objectionable side-effects can be avoided.

Very rarely will a patient with bronchospasm need more than 20 mg of methylprednisolone daily or 40 mg every other day; the every other day dosification has been shown safe in several thousands patients. In my experience, a daily or every other day early morning oral dose, combined with inhaled corticosteroids have been enough to achieve management goals, that is: relieving the spasm and decreasing the airway reactivity.

Much more recently the steroids sparing effect of several agents have been evaluated to decrease the daily or alternate day dose of corticosteroids and to reduce their side effects. Among these agents are TOM (toleandomycin), gold salt therapy and methotrexate, all of them with some success. Methotrexate may be beneficial in the treatment of asthma according to the latest report of Mullaskey et al. Still it is too early to recommend methotrexate for every patient with steroid-dependent asthma. The extent of its toxic effects have to be defined before it's widespread use.

Suggested Reading

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RESIDENCY University of California School of Medicine, San Francisco: General Surgery — 2 years; Otolaryngology — 3 years.

FELLOWSHIPS National Institute of Health Fellow; Cancer Research Institute, University of California, San Francisco.

OUTSTANDING ACHIEVEMENTS Freshman Medical Student Research Award; Class President — 2nd year medical school; Student Body President — senior year medical school; Special Award by National Institute of Health to attend and present paper at International Congress of Otolaryngology in Tokyo, Japan; Chairman, Department of Otolaryngology, San Francisco General Hospital 1970-76; Chief of Medical Staff, Franklin Hospital 1982-84.



Dr. Tipton and residents examining post-operative patient in recovery room.

“I joined the Army Reserve shortly after completing my responsibilities as Chief of Staff of Franklin Hospital in San Francisco. I was intrigued with the idea of trying something different, such as Army Medicine.

“I find that the challenges and rewards of serving as an Army Reserve physician complement my civilian practice. For a number of years, I’ve been teaching as a member of the Clinical Faculty at the University of California School of Medicine, and I thoroughly enjoy the many teaching opportunities available to me in the Reserve. It is a rewarding experience to be involved in the training of Army medical students, interns, and residents. I also enjoy interacting and exchanging information with full-time Army physicians and seeing a wide variety of interesting clinical cases.

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ABSTRACTS

AMERICAN COLLEGE OF PHYSICIANS
PUERTO RICO CHAPTER

OCTOBER 1988

1

DYNAMICS OF PTH SECRETION IN PRIMARY HYPERPARATHYROIDISM. Lillian Haddock, F.A.C.P., Juan R. Otero, MD (Assoc.), Cesar Trabanco, MD (Assoc.) and Venesa Ortiz, M.T., UPR School of Medicine

A sensitive two site immunoradiometric assay which detects only intact human PTH(1-84) was used to study the dynamics of PTH secretion in 8 subjects (6F, 2M) with primary hyperparathyroidism (PHPTH) upon the intravenous infusion of EDTA and Calcium and postoperatively. PTH levels ranged from 65 to 475 pg/ml (N: 10-65pg/ml). Upon EDTA infusion PTH increased 56 to 423pg/ml from baseline value (42 to 630% increase). There was an strong negative correlation between the serum calcium and the PTH level ($r = -0.85$). In 2 subjects in which an intravenous calcium test was performed the serum PTH decreased from 135 to 26pg/ml in one and from 142 to 63 pg/ml in the other, a limited suppression as seen in PHPTH. The level of PTH was studied postoperatively in 5 subjects (3 adenomas, 2 hyperplasia). Within 10 minutes of removal of the adenomas in 2 patients and the hyperplastic glands the PTH level was normal. It decreased to subnormal values in the 3 patients with adenomas but recovered within 24 to 48 hrs in response to the postoperative hypocalcemia. Therefore, functional recovery of atrophic parathyroid tissue is more rapid than that of other endocrine tissues. Studies on concurrent changes in the levels of 1,25 dihydroxycholecalciferol, now in progress, will be presented.

2

GASTRIC CARCINOMA AT THE HOSPITAL UNIVERSITARIO RAMON RUIZ ARNAU (HURRA) IN THE LAST DECADE.

J.A. MARQUES BIBILONI, M. PEREZ, J.C. OPPENHEIMER, M. MARCIAL SEOANE, R. HUNTER MELLADO. Universidad Central del Caribe, Bayamón, Puerto Rico.

Gastric Cancer represents a prevalent neoplasm in Puerto Rico. In efforts to define its natural history in our population, we have reviewed all cases of Gastric Ca. diagnosed in HURRA between 3/78-3/88. In this period 8 cases were identified, 7 were excluded due to lack of histology. Of the remaining 79 patients, 54 were males and 25 females. The mean age was 66y(28-86-range) with no sex differences. A relative risk ratio for the incidence of Gastric CA for the 11 towns served by HURRA was calculated with the risk ratio ranging between .038-.34. The blood group was known in 18 patients with 61% having A type and 39% type O. The TNM staging was established in 70 cases. Of these 59 (86%) were Stage 4, 5(7%) Stage 3, 4(6%) Stage 2 and 1 (1%) Stage 1. Due to the small number of patients with Stage 1-3, only patients with Stage 4 were further analyzed. The overall median survival for Stage 4 was 29 weeks with 10% achieving a 2 year survival. No differences were seen between males (26w) vs. females (31w). Of the stage 4 patients 32 received chemotherapy (FAM) and 21 no therapy. The median survival was 38 w with 11% surviving 2 years, in the therapy group vs. 6 weeks with 0% two year survival in the no therapy group. The significance of this is unclear. The performance status could not be established, thus serum albumin was selected as index of nutrition. The median survival of Stage 4 patients with albumin greater than 3gm% was 29 w as compared to 10 w in those with less than 3. Further analysis revealed that 80% of patients with albumin greater than 3 received therapy as compared to 50% in those with levels lesser than 3. We conclude that the majority of cases present with advanced disease. Differences in the relative risk ratio among our communities is suggested. The impact of chemotherapy needs to be established. This study was supported by RCMI award RR 03035-01A1 from NIH.

3

INCIDENCE AND PREVALENCE OF HIV-POSITIVE PATIENTS ON CHRONIC HEMODIALYSIS AT THE UNIVERSITY DISTRICT & SAN JUAN CITY HOSPITAL

Dennis Negron MD (Associate), Victor Arrieta MD, Libia Diaz MD (Associate), Rafael Burgos Calderon MD, Carlos Rivera MD and Francisco Joglar MD (Member ACP), University of Puerto Rico, School of Medicine Department of Medicine, Nephrology Section, Rio Piedras P.R.

There is controversy on whether or not patients with ESRD on chronic hemodialysis (HD) should be routinely tested for the presence of HIV-antibody (HIV-Ab) in their blood. Several reports have appeared in the literature reporting incidences from 0 to 11%.

A total of 227 patients (average 82 patients/month) receiving chronic HD, at the University District and San Juan City Hospital, from January to December 1987 were screened for the presence of HIV-Ab by the ELISA method. Those reported as positive were confirmed by the Western Blot method. HIV presence was reported and confirmed in 9 (4%). Five of these patients (2%) were IV drug abusers, 2 (0.9%) homosexual, 1 (0.4%) had history of sexual promiscuity and 1 (0.4%) had been exposed to multiple blood transfusion (MBT) prior to HIV testing of blood donors. Our prevalence was 7%. However when risk factors other than MBT were excluded the prevalence was 0.4%.

The incidence and prevalence of HIV positive cases in our hemodialysis population is comparable to that previously reported in the literature.

4

SEROPREVALENCE OF MARKERS OF SEXUALLY TRANSMITTED DISEASES IN A VOLUNTEER BLOOD DONOR POPULATION.

Alberto F. Fernández, M.D., and Manuel A. Marcial, M.D. (member). Dept. of Pathology and Lab. Medicine, Univ. Central del Caribe Sch. of Medicine, Bayamon, P.R.

The rates of VDRL positivity and the seroprevalence of chronic hepatitis B virus (HBV) and human immunodeficiency virus (HIV) markers in the Bayamón community are not known. We are sometimes ascribed the same high HBsAg rates seen in other Caribbean and Central American nations. Similarly, widely discrepant HIV rates are published in newspapers.

Transmission of HBV and HIV through blood and blood products has been documented. The blood-banking community has taken several steps to prevent the transfusion of these viruses. Among these is the testing of donated blood for viral markers. We used available serologic data from our Blood Bank files to determine the prevalence of such infections in our volunteer donor population. Included were four years of HBsAg and VDRL testing and three years of HIV testing. The results were as follows:

Year	Donors	HBsAg	VDRL	HIV
84-85	1070	6 (0.5%)	7 (0.6%)	-
85-86	1316	9 (0.7%)	16 (1.2%)	9 (0.6%)
86-87	1303	14 (1.1%)	17 (1.3%)	11 (0.8%)
87-88	990	12 (1.2%)	16 (1.6%)	9 (0.9%)
Totals	4679	41 (0.9%)	56 (1.2%)	29 (0.8%)

The results indicate: 1) a slow increase of VDRL positivity; 2) a clear increase of HBsAg positivity, its prevalence doubling in four years of testing; 3) a slight increase in HIV positivity. However, the marked HIV dissemination in non-risk group members, expected by some, is not reflected in these statistics. Notwithstanding, the disturbing rise in the prevalence of sexually-transmitted diseases in our donor population merits additional study. This study was supported by RCMI award #RR 03035-01A1 from the NIH.

5

FAMILIAL DYSALBUMINEMIC HYPERTHYROIDISM (FDH) A PERTINENT DIFFERENTIAL DIAGNOSIS IN P. RICO Francisco Aguiló Jr. FACP, César Trabanco (Associate) & Juan R. Detero (Assoc) Endocrinol. Div Univ. P. Rico School of Medicine, San Juan PR

Increasing availability and utilization of laboratory tests for thyroid hormone(s) circulating in plasma have resulted in detection of laboratory findings that are not in keeping with the clinical features of classical thyroid hormone derangements, yet prompt therapy for presumed thyroid dysfunction. FDH is a familial autosomal syndrome characterized by elevated serum thyroxine (T₄) and free-T₄ index due to abnormal serum albumin or pre-albumin that preferentially bind T₄. In USA, almost half of reported families have been of Hispanic/Puerto Rican origin. We have encountered 5 families with FDH in Puerto Rico during the past 2 years 2 of which contain a total of 11 affected members, and a common Corican ancestry. The proband, a 13 year-old boy had T₄ test for palpitations upon exercise and a heart murmur. An elevated value lead to Rx of antithyroid medication x 4 years. He became hypothyroid, had difficulty learning at school & developed goiter. His sister had decreased weight (while on exercise regimen) and was given imidazole. This caused irregular menses, a goiter and thrombocytopenia. An older brother and sister were similarly treated. A maternal aunt and her 4 children also had elevated T₄. In all, 4 out of 9 maternal siblings had FDH, as shown by normal TBG's [thyroxine binding globulin], radioactive iodine uptakes, TSH & clinical euthyroidism. Preliminary HLA typing point to a higher frequency of A2B39 in this family. We have begun a prevalence study among neonatal screeners to define the apparently higher prevalence of FDH in PR, a Dx to be kept in mind.

6

BENIGN HYPERGLOBULINEMIC PURPURA OF WALDENSTROM REPORT OF 7 CASES AND LONG TERM FOLLOW UP. José Lozada, MD, FACP, Norman Maldonado, MD, FACP, Jorge Sánchez, MD, Carlos Fernández, MD and Marisel Cortés, MT. Department of Medicine and Dermatology, Puerto Rico School of Medicine, Río Piedras, Puerto Rico.

In 1943 Waldenström described three females with recurrent purpura of the lower extremities, increased sedimentation rate and hypergammaglobulinemia. Since then close to 150 cases have been reported with this condition. In some instances it is associated with Sjögrens syndrome, systemic lupus erythematosus, rheumatoid arthritis and others. Circulating immune complexes composed of IgG-Anti IgG and IgA-Anti IgG have been demonstrated as well as high titers of rheumatoid factor.

Eighteen years ago we studied 5 patients who fulfilled the diagnostic criteria of benign hypergammaglobulinemic purpura of Waldenström (BHPW) and since then two additional patients have been studied. All patients are women. Mild anemia and modest granulocytopenia was present in some. Urinalysis, blood chemistries and coagulation studies were normal. Latex fixation was positive with high titers in all patients and remained unchanged. ANA was positive in three patients. Hypergammaglobulinemia and increase in IgG was present. In all patients and in three re-evaluated remained unchanged for 18 years. Platelet aggregation, Raji assay, peripheral lymphocytes cell markers, skin biopsies and immunofluorescent studies were done in some patients.

BHPW is due to an alteration in the immune system probably a deregulation of the T cell system. The benign nature of the condition even in those who have evidence of systemic lupus erythematosus was confirmed. This distinct clinical entity and the benign clinical course should be recognized.

7

LONG TERM EXPERIENCE WITH A TOTALLY IMPLANTED CATHETER SYSTEM Cesar O. Freytes, MD (member), Patricia Reid, RN and Kirby L. Smith, MD, Memphis Cancer Center, Memphis, TN

Vascular access represents a significant problem in cancer patients (pts.). A new method to circumvent this problem is to utilize a totally implanted central venous catheter system (TICS). Its subcutaneous location makes it more desirable for pts. than external catheters, requires less maintenance and the risk of sepsis and other complications are thought to be low. Previous reports on these systems consisted of small numbers of pts. with limited follow up. We retrospectively evaluated the performance and long-term complications of a TICS (Port-A-Cath). 134 systems were implanted in 128 pts. The median duration of implantation was 44 weeks (range 2 to 220) with 49 systems implanted for more than 1 year. Complications with the system included: extravasation (2 cases, 1.5%), mechanical malfunction (2 cases, 1.5%), vein thrombosis (1 case, 1%), malposition of reservoir (3 cases, 2%), clotting of the reservoir or outlet catheter (3 cases, 2%), skin infection (2 cases, 1.5%), skin perforation or wound dehiscence (2 cases, 1.5%), sepsis (1 case, 1%) and pneumothorax (1 case, 1%) for a total complication rate of 13%. Most of these complications resolved spontaneously or with medical treatment. Only 6 pts. required reimplantation of another system. No fatalities resulted from these complications. We conclude that with long term usage of the system the complication rate remains low making it a safe and viable alternative for long term intravenous therapy.

8

CORONARY ARTERY DISEASE IN PUERTORRICAN PATIENTS LESS THAN FORTY YEARS OLD.

Antonio Renta, MD, Pablo I. Altieri, MD, José A. Martínez Toro, MD, and Héctor L. Banchs, MD, Department of Medicine, University of Puerto Rico, Medical Science Campus, Río Piedras, Puerto Rico.

We reviewed the catheterization results in the last 7 years (5000 cases) looking for patients (P) less than 40 years old with coronary artery disease. Twenty five patients were found (4%). There were 20 male patients (87%) and 3 female (13%). Fourteen patients had one vessel disease. Two patients (9%) had 2 vessel disease and 7 (30%) had 3 vessel disease. The most affected vessel was the left anterior descending artery followed by the circumflex and right coronary arteries (same frequency). The risk factors in decreasing order were as follows:

- | | |
|-------------------------|-----|
| 1. Smoking | 56% |
| 2. Diabetes Mellitus | 30% |
| 3. Hypertension | 21% |
| 4. Elevated Cholesterol | 11% |
| 5. Family History | 9% |

The management consisted of angioplasty, surgery or medical therapy.

In conclusion symptomatic coronary disease in the young population in Puerto Rico is rare with only 23 patients in more than 5000 catheterizations. The most frequent risk factor is smoking followed by diabetes mellitus. A strong effort should be done in our population to instruct them about the hazards of cigarette smoking and to have good control of blood sugar in diabetes mellitus.

9

Apolipoprotein-B Levels in Inflammatory Arthritis.
Luis Vilá, MD; Rosa Llubes, MT, Edwin Mejías, MD.
San Juan Veterans Administration Medical Center,
San Juan, Puerto Rico.

A number of biologically significant proteins bind to urate crystals and may influence crystal-induced neutrophil responses. Terkeltaub found that lipoproteins containing apolipoprotein B account for virtually all of the plasma inhibitory activity in urate-induced neutrophil superoxide generation and cytolysis. To evaluate the *in vivo* effect of apolipoprotein B in the regulation of inflammatory response in gouty arthritis, patients with acute gouty arthritis and other acute inflammatory arthritis were studied. Preliminary results show no significant difference in synovial apolipoprotein B levels of patients with acute gouty arthritis, pseudogout and rheumatoid arthritis. Values obtained were 52 ± 11 mg/dl (N=6), 53 ± 11 mg/dl (N=5) and 41 ± 19 mg/dl (N=4) respectively. These patients were followed for a mean period of 8 months. Patients with acute gouty arthritis and pseudogout who had recurrent inflammatory arthritis presented lower synovial apolipoprotein B levels (42 ± 2.5 mg/dl and 31 mg/dl, respectively) when compared with patients that had no recurrence (57 ± 11 mg/dl and 59 ± 2 mg/dl respectively), suggesting a possible protective antiinflammatory effect of apolipoprotein B in later patients. One patient with active rheumatoid arthritis and recurrent episodes of inflammatory arthritis presents marked decrease of synovial apolipoprotein B levels (21 mg/dl).

10

TREATMENT OF ACUTE NON LYMPHOCYTIC LEUKEMIA (AML)-EXPERIENCE AT THE UPR SCHOOL OF MEDICINE HOSPITAL.
Wanda E. Ortiz MD, Agnes Charles MD, Carmen Falcón RN, and Enrique Vélez-García MD. Hematology/Medical Oncology Section, University Hospital, UPR School of Medicine, San Juan, PR.

Adult patients (>15) newly diagnosed as AML were treated with cytosine arabinoside (CA), $100\text{ mg/m}^2/\text{d}$ by continuous infusion for 7 days and randomly assigned to receive either idarubicin (I), $12\text{ mg/M}^2/\text{d}$, or daunorubicin (D), $45\text{ mg/m}^2/\text{d}$ by IV infusion for three days. Seven days later, bone marrow was performed; if leukemia persisted, a second course was given. If hypocellular, marrows were performed weekly until response could be determined. Those failing to achieve complete remission (CR) after 2 courses were taken off study and those achieving CR received 3 consolidation courses consisting of CA, 100 mg/m^2 IV push every 12 hours for 5 days; thioguanine, 100 mg/m^2 every 12 hours po for 5 days and either I, 15 mg/m^2 or D, 50 mg/m^2 IV on day 1 of each course. Patients completing consolidation received 4 intensification courses every 13 weeks with a 5 day infusion of CA (100 mg/m^2) plus either I, 12 mg/m^2 or D, 45 mg/m^2 on day 1 and 2 of each course. Of 32 patients, 27 are evaluable for analysis (5 died less than 14 days after induction). 19/27 (70%) achieved CR (11 after 1 course and 8 after 2 courses) and 3 obtained partial remission (PR) for a combined CR/PR=82%. Of those patients receiving I, 9/10 (90%) achieved CR. Analysis by prognostic factors including age, initial white blood cell count, FAB type and presence of sepsis at presentation failed to show significant differences. Toxicity was not different in the two schemas. Follow up data so far: 7/19 CR's have relapsed 8-32 weeks after CR; 1 was referred for marrow transplantation; 2 died in CR during consolidation or maintenance therapy and 9 are still in CR 1-46 weeks after induction. These data are encouraging and demonstrate that successful treatment of AML in our environment is possible in spite of many limitations.

11

A COMPARATIVE ANALYSIS OF AZTREONAM-CLINDAMYCIN (AzC) VS. TOBRAMYCIN-CLINDAMYCIN (TC) OR AMIKACIN-MEZLOCILLIN (AM) IN LOWER RESPIRATORY TRACT INFECTIONS CAUSED BY GRAM-NEGATIVE BACILLI.
C. Rivera-Vázquez, M.D., C. H. Ramírez-Ronda, M.D., F.A.C.P., J. Rodríguez, M.D., S. Saavedra, M.D., Member, O. Vera, B.S., M.T., B. Padilla, M.L.T., Infectious Diseases Program, VA Medical Center and UPR School of Medicine, San Juan, PR.

The clinical efficacy and safety of the regime AzC is compared to the regimes of TC or AM. Patients (PTS) with lower respiratory tract infections, documented by a lung infiltrate on a chest x-ray, leukocytosis, fever and a sputum (>25 PMN, <10 epithelial) with predominance of gram-negative bacilli (GNB) were randomized after signing an informed consent to receive AzC or TC, or receive AzC or AM. A group of 110 PTS were enrolled into the study, 83 PTS were bacteriologically evaluable. Of the bacteriologically evaluable patients, 50 received AzC, 18 TC and 15 AM. PTS on AC received 8 gms of Az and 2.4 gms of C, PTS on TC received 0.24 gms T and 2.4 gms of C and PTS on AM received 1.0 gm A and 16 gms of M on a daily basis. All groups received the antibiotics for 11-12 days. The mean age in all three groups was similar: 67 years in AzC, 62 years in TC and 59 years in AM. The clinical outcome in all groups is comparable with bacteriologic eradication in the AzC group in 46/50, in the TC 16/18 and in the AM 14/15. The most frequent isolated GNB in all groups was *K. pneumoniae*, followed by *E. coli*, *P. aeruginosa*, *Serratia*, *Enterobacter* and other aerobic GNB. All strains were eradicated, there was the emergence of a resistant *P. aeruginosa* strain to Az during treatment. There was one superinfection in the AzC group with *S. epidermidis* and *Candida*. The failures were with *P. aeruginosa* in AzC and *K. pneumoniae* in TC. The side effects found in the 3 treatment regimes were: thrombocytosis, eosinophilia and transient increases in liver function tests. In the TC and AM groups, altered renal function. The use of AzC is as effective as the regimes of TC or AM in the treatment of bacteriologically documented lower respiratory tract infections caused by aerobic GNB.

12

EXPERIENCE WITH THE ADMINISTRATION OF I.V. STREPTOKINASE IN ACUTE MYOCARDIAL INFARCT: A RETROSPECTIVE STUDY.
J.J. Vázquez-Bauzá, M.D., A.J. Quesada, M.D., E. Hernández, M.D., FACP, J. Suárez, M.D., E. Linares, M.D., FACP. Veterans Administration Hospital, San Juan, Puerto Rico.

From October 1986 to December 1987, 39 patients (pts.) with Acute Myocardial Infarction (MI) received Intravenous Streptokinase (IVSK) within 6 hours (mean 3.2 ± 1.3 hours) at the San Juan Veterans Hospital. All were male with mean age of 54.6 ± 9.7 year (range 35 to 72 yrs.). On admission 26 patients (67%) had an Acute Inferior Myocardial Infarct (IWMI). No previous MI was evidenced in 21 patients (54%), 13 of these patients had AAMI and 8 patients had IWMI.

Reperfusion was judged to have occurred, by enzymatic parameters, in 27 patients (69%), including all 6 patients with first AAMI treated within 3 hours of onset of symptoms. Adverse reactions to IVSK occurred in 3 patients (8%).

The data from patients with first infarcts was analyzed for Left Ventricular Ejection Fraction (EF) and mortality, according to infarct location and time from onset of symptom to initiation of IVSK (Group A). This group was compared to a similar group of patients seen during the same time interval who did not received IVSK (Group B).

Group A		Group B	
< 3 hours	> 3 hours		
EF $47.5\% \pm 9.9$	$32.9\% \pm 9.1$	**	$38.1\% \pm 8.8$
p < .01	p < .05		

The mortality in Group A (10%) was lower than in Group B (13.3%), but the difference did not reach statistical significance.

In conclusion, the benefit of IVSK appears to be greater in patients with AAMI when treated with 3 hours of the onset of symptoms.

13

INCIDENCE OF RETROVIRUS INFECTION (HTLVI HIV) IN HIGH RISK POPULATION Miguel Magraner, M.D., (Associate), Raúl Castillo, M. D. (Associate), and Y. Yammamura, PhD. Dana's Hospital Ponce, P. R.

HTLVI and HIV are retroviruses which are transmitted through sexual contact, from mother to fetus, and through transfusion of blood products. HTLVI has been associated with adult T Leukemia, tropical spastic paraparesis and other myelopathies; HIV is the etiologic agent of AIDS. A population at risk for retrovirus infection such as IV drug abusers, prostitutes and sexual partners of HIV patients were contacted in the community of La Playa de Ponce, and after informed consent, blood sample were performed for HTLVI and HIV titers by the Elisa Method. The group consisted of 38 subjects with a mean age of 25.7 years old and a male to female ratio of 1:1; of these groups 14/38 (37%) were positive for HIV and 5/38 (14%) were positive for HTLVI. The group with highest risk of infection were the IV drug abuser, 66% were positive for HIV, 20% for HTLVI. Four (4) patients had evidence of infection for both retroviruses.

It appears that in the area of Puerto Rico (Playa de Ponce) risk groups have high incidence of HTLVI and HIV infection. The relevance of infection with both virus is not well known, and it will be evaluated in follow up studies.

14

ESOPHAGEAL SCLEROSIS: A RANDOMIZED TRIAL COMPARING WEEKLY VS. THREE WEEKS SCHEDULE IN THE TREATMENT OF ESOPHAGEAL VARICES. Wilfredo Pagani, MD, Carlos Rubio, MD, FACP and Esther Torres, MD, FACP, University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

Patients known to have bled from esophageal varices were randomized on alternate basis to either weekly or every three weeks variceal sclerosis. Fourteen patients received weekly therapy and 14 every three weeks. The groups were similar in age, sex, etiology and severity of their liver disease. The weekly group had one failure, one death and two dropouts; in 8 total obliteration was achieved and one is still in therapy. The average time to achieve total obliteration was eleven weeks and only one rebled. Esophageal ulceration occurred in 7 of these. In the triweekly group there were two failures, 3 deaths and 5 dropouts. Four patients had major bleeding episodes. This preliminary data suggests that weekly sclerosis is superior in achieving total obliteration with better compliance and less incidence of recurrence of major bleeding; however, this was associated with a much higher evidence of esophageal ulceration.

15

Incidence of Campylobacter Pyloris at antral mucosa in patients with dyspepsia. Rafael Mosquera, M.D. (Associate), Carmen González Keelan, M.D., Esther A. Torres, M.D., F.A.C.P. Departments of Medicine and Pathology, University of Puerto Rico, School of Medicine.

To determine the prevalence of *C. Pyloris* in our population and its relation to mucosal disease, all patients referred for elective endoscopy at UDH from January 1988 to May 1988 were included in the study except those with esophageal or gastric cancer or gastric surgery. Four quadrant antral biopsies were examined for histology and campylobacter identification. A total of 58 patients with dyspepsia were examined, 23 male and 35 female (mean age 50 y/o). Fifty percent of these patients were found with gastritis (29 out of 58), 9 out of 58 were found with duodenal ulcer (15%), 18 out of 58 had gastric ulcer (31%) and 11 out of 58 had a normal endoscopy (19%). *Campylobacter* was found to be present in 86% of patients with gastritis, in 88% of patients with duodenal ulcer, in 83% of patients with gastric ulcer and in 63% of patients with normal endoscopies. Histological examination of normal endoscopies showed evidence of acute gastritis in 8 of 11 patients (72%). Of these, 75% were *C. pylori* positive, 1 was non diagnostic, and the other 2 negative. Two patients with normal endoscopy and histology were *C. pylori* negative. In conclusion, the incidence of *C. pylori* in antral mucosa of GI patients with duodenal ulcer, gastric ulcer or gastritis is similar to the ones reported in literature (88%, Graham et al).

16

COMPARATIVE RANDOMIZED STUDY OF CIPROFLOXACIN IV VS CEFTAZIOIME IN THE TREATMENT OF SERIOUS INFECTIONS: RESULTS OF THE FIRST 40 PATIENTS. C. Rivera-Vázquez, M.D., S. Saavedra, Member, and C. H. Ramirez-Ronda, M.D., F.A.C.P., Infectious Diseases Research Lab., Infectious Disease Program, San Juan VAMC and Univ. of Puerto Rico School of Medicine, San Juan, PR.

A study was designed to compare the effectiveness and safety of ciprofloxacin (CIP), 400 mg IV daily, with ceftazidime (CEF), 3 grams IV daily, in the treatment of documented serious infections utilizing a blinded investigator. A total of 40 patients (PTS) were enrolled after signing an informed consent form. Twenty were randomized to each group. In the CIP group the mean age was 59.6 years; there were 20 clinically and bacteriologically evaluable PTS. In the CEF group the mean age was 61.8 years and there was an identical number of evaluable PTS. The mean duration of treatment was 10.4 days in CIP and 10.3 days in CEF. There were 42 infections treated in the 40 PTS, one patient in each group had two infection sites. Most of the infections, 20/21 in each group, were serious soft tissue infections; there was one pneumonia in CIP and 1 peritonitis in CEF (6 GMS). The etiologic agents recovered were comparable with a total of 29 strains recovered from the CIP PTS and 35 from the CEF PTS; the number of gram positive, gram negative, and mixed infections were comparable in both groups, except for anaerobes in the peritonitis patient on CEF. All aerobic microorganisms were susceptible to CIP and CEF. The underlying medical conditions were comparable in both study groups. In the CIP group 16/21 infections were clinical cures and 2 failures; in the CEF group 14/21 were cures and 4/21 were failures. There was bacteriological eradication in 19/21 infections on CIP and 16/21 in CEF; there was persistence of 2/21 in CIP and 3/21 in CEF. There was one recurrence with group A streptococci in CIP and 2 recurrences, *S. aureus* and *C. diversus* on CEF. There were no superinfections. One strain of *E. cloacae* became resistant to CEF during treatment. In the treatment of serious soft tissue infections CIP IV is comparable to CEF IV. There is a tendency for persistence of aerobic gram-positive cocci in the CIP group, this requires further evaluation.

17

EVALUATION OF SILENT MYOCARDIAL ISCHEMIA ON DIABETIC PATIENTS. Osvaldo A. Figueroa, MD, Manuel Quiles, MD, Edgardo Hernández, MD. Veterans Administration Hospital, San Juan, Puerto Rico.

Coronary Artery Disease (CAD) is the leading cause of death in diabetics (D). Several reports have documented a greater incidence of CAD among D compared to non-diabetics and showed that once it turns symptomatic both short and long term prognoses are poorer in D. The detection of myocardial ischemia in D without previous manifestations of CAD has not been fully explored. This may be of help in the clinical management of these patients. We used Treadmill Exercise Testing (TMT) and 24 hr. Holter monitoring (H) in a group of 21 asymptomatic D patients without know CAD in an attempt to detect the prevalence of silent ischemia (SI). Seventeen D patients had both TMT and H, 3 patients had TMT only and 1 patient had H only. All patients were males, and the mean age was 59.7. Seven patients were hypertensives (33%) and 7 (33%) were smokers. There was 1 (5%) ischemic electrocardiographic response on TMT but none by H. Sixty percent (13/20) of the patients had a hypertensive exercise response during TMT and 22% (4/18) had significant ventricular ectopy during H monitoring. We conclude that: The prevalence of SI in this selected group of diabetics appears to be low as detected by TMT and H. A high proportion of the patients had significant ventricular ectopy. A hypertensive response during TMT is frequent.

18

HYPOLYCEMIA AS MANIFESTATION OF SEPSIS Sonia Santiago, M. D., Rouseline Valentin, M. D., Ismael Rodriguez, M. D. Damas H. Roca, P.R.

Sepsis is usually associated with hyperglycemia. Recently hypoglycemic has also been reported. A retrospective survey revealed eight patients who fulfilled the criteria of hypoglycemia (serum glucose 50 mg/dl), in the clinical setting of sepsis. Two types of patients were seen, Group I, 5 patients who had no apparent explanation for their hypoglycemia other than sepsis. Group II consisted of 3 patients, one alcoholic and 2 had Congestive Heart Failure.

Clinical disease in these patients included Pneumonia in 3 cases, UTI in 3 patients and in two patients no focus of infection was apparent. The most common features of all of these patients were leukocytosis in 5 patients, leukopenia in 3 cases, fever, metabolic acidosis and altered medical status. The blood glucose values range between 8mg/dl to 50mg/dl.

Several theories has been suggested: Consumption of glucose by bacteria, endotoxin of gram negative bacteria, lactic acidosis and metabolic acidosis. The finding of hypoglycemia in association with sepsis is not as rare a finding as believed. The importance of recognizing this entity is evident due to the high morbidity and mortality of not treating hypoglycemic on time.

19

ANALYSIS OF APLASTIC ANEMIA (AA) AT THE HOSPITAL UNIVERSITARIO RAMON RUIZ ARNAU (HURRA). Jennifer C. Oppenheimer Catala, M.D., Mirta Perez, R.N., Robert F. Hunter Mellado, Universidad Central del Caribe, Bayamon, P.R.

Aplastic anemia is a disorder characterized by cytopopenia and a hypocellular or acellular bone marrow (BM). We reviewed all cases of AA diagnosed at HURRA between 1981-1987. A total of 15 cases were identified of which 7 were excluded due to incorrect diagnosis. Of the remaining 8 patients, 2 groups were identified; Group I consisted of 6 patients with severe disease and Group II of 2 patients with moderate disease (IAASG). Group I was characterized by young individuals median age (27.5), range (17-65), all male with severe reduction in all 3 major cell lines. Four of 6 patients were treated with androgens as main therapy with 3 of 4 failing to achieve any response. The remaining 2 patients were treated with anti-thymocyte globulin (ATG) with one partial hematologic response. Median survival in this group of patients is 10 weeks with 3 of 6 patients dying within the first 10 weeks after diagnosis.

Group II consisted of 2 patients ages (61, 69) both treated with androgens and both achieving partial hematologic response.

When the 4 responders from both groups are analyzed 3 of them had BM cellularity greater than 5% and all are alive at this time. The hematologic response in the androgen treated patients is primarily confined to the erythroid cell line.

We concluded that severe AA remains a lethal disease with a high risk of death within 3 months after diagnosis. In addition, response to androgen therapy usually occurs in patients with BM cellularity greater than 5% and are usually confined to the erythroid elements.

20

SERUM CHOLESTEROL LEVELS IN PUERTO RICAN MALE VOLUNTEER BLOOD DONORS. Manuel A. Marcial, M.D. (Member), Alberto F. Fernández, M.D., and, Alba S. Bula, M.T., Dept. of Pathology and Lab. Medicine, Universidad Central del Caribe School of Medicine, Bayamón, P.R.

Elevated serum cholesterol is one of the major risk factors for coronary heart disease (CHD). Recent data have shown that USA "statistically normal" total cholesterol (T.C.) levels can no longer be considered to be "clinically normal" since they are substantially higher than the presently recommended ideal level of less than 200 mg/dl. We sampled our healthy male volunteer blood donor population to evaluate how far their T.C. levels were from the optimal values. Tests for T.C., triglyceride (TRG), and HDL cholesterol levels were analyzed using two different chemistry analyzers with a good correlation between the values obtained. LDL cholesterol levels were estimated based on the formula $LDL = T.C. - HDL - TRG/5$. Results were as follows:

Age	T.C.	HDL	LDL
20-30 yrs. (n=45)	205±97	35±17	134±69
30-40 yrs. (n=50)	197±79	39±19	126±75
40-50 yrs. (n=25)	206±100	34±12	128±79
50-65 yrs. (n=15)	189±69	37±17	144±92
Total (n=135)	200±92	36±17	131±76

Values expressed as mean ±2St. deviations in mg/dl.

46% of our volunteers had T.C. levels over 200 mg/dl, 30% had levels over 220 mg/dl, and 17% had levels over 240 mg/dl. Using the Lipid Research Clinic's recommended action values we can conclude that 30% of our donors are to be considered in the moderate risk group for CHD while 17% fall in the high risk group category. Thus, lipid profile analysis is recommended for our Puerto Rican male population as part of our effort to prevent CHD. This study was supported by RCMI award RR 03035-01A1 from NIH.

21

HEMATOLOGIC ABNORMALITIES IN HIV INFECTION. Yamil Kouri, MD, Ingrid Soderlund, MD, Luis Báez, MD. San Juan VA Medical Center, San Juan, Puerto Rico.

We studied several hematologic parameters in 109 patients seropositive for the HIV virus seen at San Juan VAH. 97 of them had been admitted a total of 142 times. Risk factors for HIV infection were: Intravenous drug abuse (IVDA) 74%, homosexuality (HS)-12%, both IVDA and HS-2%, Blood transfusions-6%, and undetermined-6%. Immune thrombocytopenic purpura (ITP) was seen in 6% of cases, a prolonged aPTT such as seen in lupus like anticoagulant was detected in 3% of patients 1% had a false positive VDRL, and hypergammaglobulinemia was found in 16%. We also examined all the Bone Marrow Aspirations (BMA) (91) on 64 hospitalized patients with positive HIV serology from 1983 to 1987. Indications were: 32% fever/sepsis, 23% suspected or known lymphoproliferative disorders, 19% thrombocytopenia, 11% other cytopenias. At the time of the BMA patients were classified as AIDS (37%), ARC (34%), ITP (14%), and no information was available in 17%. Some preliminary findings include: Plasmacytosis (17%), Erythroid hyperplasia (45%) and Lymphocytosis (42%). Histoplasma Capsulatum was directly identified in 3% of patients.

22

ACUTE PULMONARY HISTOPLASMOSIS: A HAZARD OF MARIHUANA PLANTS HUNTERS. José Ramírez Rivera, MD, FACP, University of Puerto Rico School of Medicine and the Industrial Hospital, Río Piedras, Puerto Rico.

Acute histoplasmosis has not been previously associated with the uprooting of marihuana plants. Treatment is frequently delayed because the infection is not recognized and antifungal therapy is relatively toxic.

Two policemen (PM) uprooted a 500 meter marihuana patch in a remote hill near Lares. Another 2 PM packed a truck with sacks filled with the uprooted plants. Five to ten days later the 4 PM developed fever, malaise and hacking cough. The 2 PM who packed the truck had scattered micronodular infiltrates, became afebrile after 4-5 days and returned to work. The 2 PM who uprooted the plants were hospitalized with massive progressive micronodular infiltrates: Five weeks after exposure (AE) fever, bilateral crackles and moderate hypoxemia persisted. One policeman (#1) was treated with 200mg daily of ketoconazole daily. In both fever abated and crackles disappeared within 4 days. A week later both were discharged. Fourteen weeks AE #1 had a decreased vital capacity (VC) but no crackles. The untreated policeman (#2) had recurrent fever, weight loss and bilateral crackles; ketoconazole 200mg daily was initiated for #2. Five months AE #1 had normal lung functions and a negative gallium scan. Number 2 had no systemic complaints but a loss of 25% of the VC and the gallium scan remained positive.

Complement fixation titers as high as 1:256 have reached near normal levels in all patients.

Acute histoplasmosis is a hazard of uprooting marihuana plants. Prompt treatment with ketoconazole may prevent loss of functioning lung tissue and possibly dissemination in progressive pulmonary histoplasmosis.

23

ASSOCIATION OF GASTRIC CAMPYLOBACTER LIKE ORGANISM WITH ANTRAL GASTRITIS AND DUODENAL ULCER AMONG MALE VETERANS IN PUERTO RICO.

Doris H. Toro, M.D. (Associate), Evelio F. Bravo-Fernandez, M.D. (Member), Manuel A. Marcial, M.D. (Member) and Carmen Gonzalez, M.D., Departments of Medicine and Pathology Veterans Administration Hospital, UPR School of Medicine and UCC School of Medicine. San Juan, Puerto Rico.

We attempted to verify if the reported association of gastric campylobacter like organism (GCLO) with active antral gastritis (type B gastritis) holds true in our male veterans.

We evaluated the patients undergoing elective gastroscopy at our hospital and selected all of those who did not have gastric cancer or antrectomy. Endoscopy with antral biopsies was performed on 100 consecutive patients. Biopsy specimens were examined blindly for inflammatory activity (epithelial invasion by neutrophils) and intestinal metaplasia (presence of Goblet and Paneth cells) in H & E stained slides. The presence of GCLO was determined by the acridine orange fluorescence technique, a highly sensitive and specific method.

The 137 antral biopsies examined were classified in the following histopathologic diagnosis: Active gastritis (79), Chronic gastritis with activity (24), Chronic gastritis without activity (12) and no evidence of gastritis (20). GCLO were identified in 84% (87/103) of the biopsies with inflammatory activity (Active gastritis and Chronic gastritis with activity). However GCLO were identified in only one out of 12 biopsies with intestinal metaplasia without activity. There were 16 patients with duodenal ulcer. Of these, GCLO were identified in 94% (15/16) of the antral biopsies. Our findings are consistent with previous studies in which approximately 75% of patients with gastritis and 77% of those with duodenal ulcer had GCLO identified in the antrum (Blaser, M.J. Gastroenterology 1987;93:371-83).

We conclude that the association between the presence of GCLO, active antral gastritis and duodenal ulcer holds true in our veterans.

The study was partially supported by RCM award RR 03035-01A1 from NIB

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A RANDOMIZED BLINDED COMPARISON OF ENOXACIN VS INDANYL CARBENICILLIN IN THE TREATMENT OF CHRONIC BACTERIAL PROSTATITIS. J.L. Santana, M.D., B. Padilla, L.T. and C.H. Ramirez-Ronda, M.D., F.A.C.P., Inf. Dis. Program, San Juan VAMC and University of PR School of Medicine, San Juan, Puerto Rico.

A group of 30 male patients (PTS) with a mean age of 54.4 years (32-74) and a diagnosis of chronic bacterial prostatitis (CBP) after signing an informed consent were randomized to receive enoxacin (E) 400 mg/day or carbenicillin (C) 764 mg/day for 28 days. Patients were followed at intervals and at 5-7 days and 1 month post treatment. A total of 15 PTS were randomized to E, 12 were bacteriologically documented. The pathogens were *S. epidermidis* (6), *E. coli* (3), *Enterococcus* (2), *S. aureus* (1), *Enterobacter* (1). Of the 15 PTS randomized to C all were bacteriologically evaluable. The pathogens were *S. aureus* (5), *E. coli* (3), *S. epidermidis* (2), *Klebsiella* (2), *Enterobacter* (1), *Pseudomonas* (1) and *Enterococcus* (1). Clinical cure was seen in 7/15 and 6/15 in E and 4/15 and 5/15 in C at 5-7 days and 1 month post treatment respectively. Improvement was seen in 4/15 and 3/15 in E and 8/15 and 4/15 in C at the two time periods. There were 1/15 and 2/15 failures in E and 3/15 and 5/15 in C, at 5-7 days and 30 days post treatment. Bacteriologic results were as follows: In the E group eradication of 10/12 pathogens and in the C group of 13/15 pathogens. There was one failure each in E and C, one pt. was lost to follow up in C and 1 pt. in E was discontinued because of side effects. Side effects were few, flatulence and loose stools one in each group, transient elevation of SGOT in 1 pt. receiving E and one undocumented rash in E. In the treatment of CBP E seems to be as effective as C in bacteriologic eradication. Clinical response was slightly better in the E group. E a new quinolone may offer therapeutic alternatives in the treatment of CBP.

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COMPARATIVE IN VITRO ACTIVITY OF LOMEFLOXACIN WITH OTHER QUINOLONES AGAINST 105 CLINICAL STRAINS OF *NEISSERIA GONORRHOEAE* (NG). S. Saavedra, M.D., (Member), C. Rivera-Vazquez, M.D., B. Padilla, L.T. and C.H. Ramirez Ronda, MD, F.A.C.P. Infectious Diseases Program, San Juan VAMC and University of Puerto Rico School of Medicine, San Juan, Puerto Rico

The in vitro activity of lomefloxacin (LOF) was compared to the activity of norfloxacin (NOR), ciprofloxacin (CIP) and enoxacin (ENO) against 105 clinical strains of NG, including 25 PPNG strains, 19 CMRNG strains and 61 strains of penicillin-susceptible NG. Susceptibility was determined in duplicate using the agar dilution method with proteose-hemoglobin-isovitallex agar. The results expressed as MIC₉₀ were as follows:

		MIC ₉₀ ug/ml			
	PEN	LOF	NOR	CIP	ENO
NG	0.5	0.12	0.03	0.008	0.06
CMRNG	4.0	0.12	0.25	0.015	0.06
PPNG	8.0	0.12	0.06	0.004	0.06

The in vitro activity of LOF for CMRNG strains is comparable to NOR and ENOX but lower than CIP. For penicillin-susceptible and PPNG strain LOF is comparable to ENOX but lower than NOR or CIP. The in vitro activity of LOF against NG merits the investigation of this agent in comparative clinical trials with other quinolones in the treatment of NG infections.

26

URINE N-ACETYLGLUCOSAMINIDASE (NAG) AND EDTA INFUSION AS SCREENING TEST FOR LEAD (Pb) TOXICITY IN PATIENTS WITH GOUT. Héctor Molina, MD, Rosa Llubes, MS, M. Martínez-Maldonado, MD, FACP, Edwin Mejías, MD

It has been proposed that Pb is a cause of nephropathy in patients with gout; NAG has been shown to be a marker of renal tubular damage in chronic Pb intoxication. The usefulness of the EDTA Pb mobilization test and urine NAG in patients with gout, was evaluated and used to assess the relationship between gout nephropathy and lead. Patients with gout and normal renal function, (n=9) and with gout and renal insufficiency (n=7) were studied. Urine collection for creatinine clearance, total protein, uric acid and osmolality, one day prior to and within one week after the lead mobilization test, was done. Urine NAG was measured pre and post EDTA. No difference in NAG values was found between patients with gout and normal renal function and those with gout and renal insufficiency. No difference in mobilizable Pb was found; a correlation between creatinine clearance and mobilizable Pb was not demonstrable. One patient had high urine levels of Pb. Neither NAG or EDTA infusion lead mobilization test provided evidence that Pb intoxication is responsible for renal dysfunction in patients with gout.

27

ADENOCARCINOMA OF THE JEJUNUM. Román Vélez, MD, José García, MD, and Gilberto Rodríguez, MD. Departments of Pathology and Surgery, Carolina Area Hospital, University of Puerto Rico School of Medicine, Carolina, Puerto Rico.

Adenocarcinoma of the small bowel is relatively rare. The average age for patient with jejunal carcinoma in one series was 47.8 years.

We report two cases diagnosed and operated in the Federico Trilla Hospital in Carolina, Puerto Rico. One was a 33 years old female and the other was a 31 years old male.

Presenting symptoms, management and review of the literature will be presented.

28

THE USE OF NIFEDIPINE IN PATIENTS WITH ISCHEMIC HEART DISEASE AND LEFT VENTRICULAR DYSFUNCTION. Pablo I. Altieri, MD, Joe Martínez Toro, MD, Héctor L. Banchs, MD, Department of Medicine Science Campus, University of Puerto Rico, Río Piedras, PR.

The hemodynamic effect of 10mgs of sublingual nifedipine were studied in 13 patients (9 with atherosclerotic heart disease and 4 with congenital heart disease). After 30 seconds it was noticed an increase in the heart rate from 77 beats/min. to 82 beats/min. ($P < .005$). The end diastolic volume as increased from 161cc + 50 to 164cc + 52 ($P < .005$). The end systolic volume was decreased from 81cc + 32 to 70cc + 29 ($P < .005$) and the ejection fraction increased from 50% + .90 to 57% + .10 ($P < .005$). The peak systolic pressure was decreased from 131mmHg + 19 to 126mmHg + 22 (N.S), while the peak systolic pressure/end systolic volume ratio (mmHg/cc) increased from 2.02 + 1.3 to 2.2 + 1.1 (N.S). A marked dilatation of the coronary arteries was noticed.

In conclusion the use of sublingual nifedipine produced an increase in heart rate ejection fraction and peak systolic pressure/end systolic volume. These changes accompanied by the coronary vasodilatation are highly beneficial in patients with coronary disease and congenital heart disease because the left ventricular function is markedly improved.



SOCIOS NUEVOS

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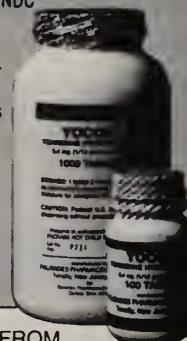
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REPORT SUGGESTS SILICONE BREAST IMPLANTS ASSOCIATED WITH CONNECTIVE TISSUE DISEASE

A study in JAMA reports further evidence suggesting a possible association in some patients between silicone breast implants and scleroderma, a potentially serious connective tissue disease that effects the skin and can damage other organs.

Of 113 new cases of scleroderma seen by the author, Harry Spiera, MD, of the Mount Sinai School of Medicine, New York City, during a seven-year period of his private practice, five (4.4 percent) had silicone breast implants two to 21 years prior to diagnosis. In contrast, only one (0.3 percent) of 286 new rheumatoid arthritis patients Spiera had seen during the same interval had silicone implants.

This statistically significant difference suggests that finding five patients with silicone implants out of 113 new scleroderma cases probably was not due to chance alone, Spiera says. Although emphasizing that a cause and effect relationship has not yet been established, Spiera says his findings and reports by others suggest that such an association may exist between silicone implants and the connective tissue disease.

Scleroderma is a chronic condition that thickens and hardens the body's connective tissues by making them fibrotic. The skin of the patient's face and limbs usually becomes shiny and rigid. The range of finger and limb movements may become limited by the tightening and rigidity of the skin. Patients often suffer joint pain and poor blood circulation in their fingers and toes. Involvement of the esophagus leads to difficulty in swallowing and involvement of the digestive tract may interfere with the absorption of nutrients. Early death can result if the heart, lungs, or kidneys become affected, the author says.

Some of the symptoms in one of Spiera's patients, whose lungs were affected, slowly improved after her implants were surgically removed, he reports. Not enough is known to justify the routine removal of breast implants in patients with scleroderma, he says. "However, if a patient becomes ill with a possibly life-threatening

disease, this certainly offers a reasonable therapeutic alternative," he adds.

The author discusses possible mechanisms that may explain how silicone implants could lead to the development of scleroderma. One hypothesis is that small amounts of silicone released by the implants into surrounding tissues may be turned into silica. Macrophages (scavenger white blood cells) that ingest silica have been shown to release factors that increase the production of collagen by connective tissue cells. Such a mechanism could explain how long-term exposure to silicone could lead to the systemic fibrosis seen in patients with scleroderma. Another possibility that has been suggested is that silicone might trigger an autoimmune disease, he says.

Four of Spiera's five patients had first been diagnosed by rheumatologists and/or dermatologists. "None of the physicians, however, had noted the presence of the silicone implants or recognized any association," he points out. "It is therefore possible that the association between silicone implants and scleroderma may be more common than has been previously appreciated." The author says that approximately 100,000 breast implants are done annually in the United States, and other silicone implant procedures, such as penile implants, are also being done with increased frequency.

"Since some of the patients who develop scleroderma following silicone implants do not do so until many years have elapsed, the full impact of the association may not yet be apparent," he concludes. "It is important that plastic surgeons, rheumatologists, dermatologists, as well as primary care physicians be aware of the possible association."

JAMA July 8, 1988

POTENTIALLY FATAL REACTION TO CARBONLESS COPY PAPER

The use of carbonless copy paper may lead to potentially fatal edema of the larynx in some susceptible persons, says a report in JAMA. Frank P. LaMarte, MD, of the University of Iowa College of Medicine, Iowa City, and colleagues studied two women who suffered recurrent episodes of hoarseness, cough, flushing rashes, and itching after handling the paper. When one of the paper's chemical ingredients (alkylphenol novalac resin) was applied to their arms, they experienced hoarseness and angioedema of the arm. One woman's plasma histamine level was six times higher than the level before testing, and examination of her larynx showed marked swelling of her vocal cords. Physicians should carefully evaluate symptoms associated with handling carbonless copy paper since such acute systemic reactions could prove fatal in susceptible individuals, the authors conclude.

JAMA July 8, 1988

SURGICAL PROCEDURE FOR NEAR-SIGHTEDNESS EVALUATED

A 35 member AMA science review panel reports "a lack of consensus" about the safety and especially the effectiveness of radial keratotomy (RK), a surgical procedure for improving myopia (near-sightedness). "Concerns about effectiveness focused on the lack of predictability of the results and the continuing change in the refractive error following surgery," says the Diagnosis and Therapeutic Technology Assessment report, published in JAMA. As the magnitude of the pre-operative eye problems increased, so did the panel's concern. Panelists also expressed concern about daily fluctuations reported in the treated eye's refractive powers, although one panelist added that most patients found freedom from glasses or contact lenses outweighed minor fluctuations in visual acuity. Nevertheless, a majority of the panelists agreed that RK may be indicated for "some carefully chosen patients" with lesser degrees of myopia and "who regard their myopia as a sufficiently severe handicap." JAMA July 8, 1988

SEVERITY OF ITCHING RELATED TO PSYCHIATRIC SYMPTOMS IN PSORIASIS

A study in July's *Archives of Dermatology* reports finding a direct relationship between the severity of itching and symptoms of depression in patients with psoriasis. Madhulika A. Gupta, MD, FRCP(C), and colleagues at the University of Michigan Medical Center, Ann Arbor, studied 82 psoriasis inpatients, 55 of whom reported moderate or severe itching. Patients reporting more severe itching upon admission had psychological test scores consistent with mild to moderate clinical depression; improvement in itching over the course of treatment was associated with an improvement in some of the features of their depression, the authors say. "Our study suggests that many of these patients should respond to specific treatments for depressive illness, such as antidepressant medications and psychotherapy, and to interventions aimed at engaging them in social activity, such as group therapy," they conclude. "These interventions will probably be of some aid in the prevention of the exacerbation of psoriasis once the patients are no longer receiving aggressive treatment in an inpatient setting."

PREVENTING SWIMMING POOL DROWNINGS; TREATING COLD-WATER DROWNING VICTIMS

Nearly one in two drowning deaths in Los Angeles County occurs in private swimming pools, pointing to the need for better prevention efforts, especially where young children are concerned, says a report in JAMA.

But such efforts must be adapted to the needs of specific localities, say the study's authors, Patrick W. O'Carroll, MD, MPH, now at the Centers for Disease Control, Atlanta, and colleagues. LA County's incidence of drownings in private pools (44.5 percent) is nearly five times the national figure of 10 percent, they note, concluding that public health professionals cannot rely on national data to develop local drowning prevention strategies.

The authors studied drowning deaths in the county from 1976 to 1984, trying to determine whether certain sites pose a higher risk for particular age groups. Risks for different sites varied dramatically with age and sex, but private pools ranked as the major drowning site for both sexes and for almost every age.

"Drowning has become an accident of affluence," comments James P. Orlowski, MD, of the Cleveland Clinic Foundation, Cleveland, Ohio, in an accompanying editorial. "Drowning is now the second leading cause of accidental death in children and the second leading cause of years of potential life lost." In addition, it is estimated that one third of near-drowning accidents result in moderate to severe brain damage from anoxia, he says.

The high fatality rate and extensive neurological morbidity associated with drowning accidents mandate that prevention rather than treatment must be the primary health strategy for drowning, O'Carroll and colleagues say. Priority should be given to preventing drownings of toddlers, 89 percent of which occur in private pools in LA County. The study notes inadequate coverage and enforcement of laws on proper pool fencing, which "has been estimated to reduce swimming-pool drowning rate by from 50 percent to as much as 90 percent."

The authors also make some related recommendations. The number of bathtub-drowning victims under age 2 suggests "parents may be overestimating the ability of infants 9 months of age and older to care for themselves in the bathtub," they say. The incidence of infant drownings in hot tubs and whirlpools suggests manufacturers need to warn customers of risk and need for adequate protective barriers. They recommend doctors alert parents with infants to these issues.

In a related report, Robert G. Bolte, MD, of the Primary Children's Medical Center, Salt Lake City, and colleagues describe the longest submerged near-drowning victim known to have survived with good neurologic recovery. The 2 1/2 year old girl was treated with a procedure called extracorporeal rearming (ECR), in which her blood was warmed and oxygenated outside her body. The authors believe she is the first child with accidental hypothermia successfully treated with ECR. The longest submersion previously reported was 45 minutes, they say.

The girl, submerged in a frigid creek for at least 66 minutes, received cardiopulmonary resuscitation for more than two hours before undergoing ECR. Tubes were inserted in her right femoral artery and right femoral vein. For 53 minutes, her blood was shunted to a device where it was oxygenated and gradually warmed until the core temperature of her body rose from 19 to 37 degrees Celsius. "The child's neurologic course showed gradual but steady improvement," the authors write.

Although she has experienced tremors, at the time of the report a year after the incident, her neurological functioning was closed to her age level. "The present report demonstrates the ECR can be effectively and rapidly employed in small children," the authors conclude.

In his editorial, however, Orlowski urges tempered enthusiasm toward such miraculous recoveries. "Most cases of poor outcome after ice-water submersions were probably not reported, whereas cases with an excellent outcome after prolonged submersion are readily published," he writes. "The factors that determine good or poor outcomes in ice-water-submersion accidents have not yet been elucidated," he says. "The optimal treatment of victims remains unresolved." More extreme measures such as ECR should be reserved for patients whose heart will not restart with more conservative resuscitation procedure, he says.

JAMA July 15, 1988

SEVERE HIPOGLYCEMIA RISK IN PENTAMIDINE USERS

Higher doses and longer-term therapy with pentamidine isethionate, a drug often used to treat AIDS-related pneumonia, increases the risk of patients suffering serious, potentially fatal, hypoglycemia, says a report in JAMA.

Hypoglycemia associated with pentamidine therapy was first reported in 1943. Since then, numerous cases have been reported, including the 1984 deaths of three patients receiving the drug for treatment of *Pneumocystis pneumonia*, says the study by Hetty Waskin, MD, now with the Duke University Medical Center, Durham, NC, and colleagues. Risk factors for this potentially fatal reaction have been unclear, however, the report notes.

The Centers for Disease Control, Atlanta, was the sole source of pentamidine in the United States from January 1967 to October 1984, under an investigational release by the Food and Drug Administration. One of the drug's key indications during this period was for the rare *Pneumocystis carinii* pneumonia, the parasitic infection characteristic of AIDS but also seen in other immunodeficiencies.

The authors reviewed records of 164 patients treated with pentamidine at 15 New York City hospitals in 1984; 97 percent of these had been diagnosed with AIDS. Hypoglycemia was reported in 23 patients (14 percent), and was more likely to occur in patients receiving therapy of longer duration and of increasing dosage. Recurrent pentamidine treatment also increased the risk of hypoglycemia, as did the occurrence of azotemia, the researchers say.

The authors report the incidence of fatal hypoglycemia in patients receiving pentamidine in the United States in 1984 to be 13 per 10,000—three patients out of 2,231 treated. These three included two adults with AIDS and an infant with another immune disorder.

However, this number "may under-represent the true incidence of this reaction, as fatal reactions from hypoglycemia may be obscured by the substantive mortality of acute *Pneumocystis pneumonia*," they say. "Early identification of risk factors that place patients at greatest risk for hypoglycemia is important to anticipate and promptly treat this life-threatening reaction."

"Patients at particular risk for hypoglycemia are those receiving prolonged or recurrent (pentamidine) therapy," the researchers conclude. "Thus, prospective studies that evaluate the efficacy of a lower dose and a shorter duration of pentamidine therapy will be important to decrease the cumulative doses of the drug and lessen the risk of serious, potentially fatal, hypoglycemia."

JAMA July 15, 1988

LOVASTATIN VERSUS CHOLESTYRAMINE FOR HYPERCHOLESTEROLEMIA

Lovastatin, a new lipid-lowering drug that works by disrupting cholesterol-synthesis, is both more effective and better tolerated than cholestyramine in treating primary hypercholesterolemia, says a study in JAMA. The multi-center study, coordinated by the Merck Sharp & Dohme Research Laboratories, Rahway, NJ (Merck makes lovastatin), involved 264 patients with elevated low-density lipoprotein (LDL) levels who took either 12 grams of cholestyramine (a bile acid-binding resin often used as first line therapy in hypercholesterolemia), 20 mg of lovastatin or 40 mg of lovastatin twice a day. Both drugs substantially reduced total plasma cholesterol by lowering LDL, but lovastatin was considerably more effective, particularly at the 40 mg level, where the mean total plasma cholesterol reduction was twice that seen with cholestyramine, the authors say. Patient compliance with therapy was better in those taking lovastatin, which was more convenient and caused fewer reported gastrointestinal problems than cholestyramine, they say.

JAMA July 15, 1988

CMV TRANSMISSION AND CORNEAL TRANSPLANTATION

Cytomegalovirus (CMV) transmission from infected donors is a major concern in most organ transplant cases, since it can cause serious problems when recipients' immune systems are suppressed to control rejection. But CMV is not a hazard in corneal transplantation as long as patients have normal immune function, so donor corneas should not be rejected based on CMV status, a letter in July's *Archives of Ophthalmology* says. Maureen G. Maguire, PhD, of the federally sponsored Collaborative Corneal Transplant Studies, Baltimore, says her group

studied the CMV antibody status of 39 donors and 49 corneal transplant recipients, and found pre-transplant CMV exposure was common. Seroconversion occurred in some recipients *without* apparent infection through donor corneas, yet there were no reports of CMV-related disease among study patients. "The risk associated with CMV for the patient receiving a corneal transplant is extremely small, especially when compared with the benefits of successful transplantation," she concludes.

MEDICAL AND ECONOMIC COST OF INTENTIONAL INJURIES

Intentional injury accounts for an increasing proportion of trauma cases in the United States and an increasing economic burden on treatment centers, a report in July's *Archives of Surgery* says. The report's authors, Gregory K. Luna, MD, of the University of Washington School of Medicine, Seattle, and colleagues followed up all victims of intentional injury admitted during one year at Seattle's Harborview Medical Center, a regional trauma center. Seventeen percent of the 2,451 trauma patients admitted were victims of nonaccidental injury; the majority were severely injured. Hospital charges averaged \$13,000 per patient, with three-fourths requiring governmental funding for medical care. Six months after the authors finished their review, only two-thirds of all expenditures had been reimbursed. "These patients represent a high medical services use group and consume a disproportionately high percentage of medical resources," they say.

DRGs' IMPACT ON MALNOURISHED PATIENTS

Head and neck cancer patients are at high risk for malnutrition, and a report in JAMA suggests that malnourished patients undergoing major surgery for these malignancies don't do as well under the diagnosis related group (DRG) reimbursement system. Authors Bernard S. Linn, MD, and David S. Robinson, MD, of the Veterans Administration Medical Center, Miami, and University of Miami School of Medicine, theorized that malnourished patients would be less well-nourished at the time of surgery due to DRG-shortened preoperative stays, and thus have more postsurgery complications. Their study involved 120 male head and neck cancer patients admitted for surgery—59 before DRGs were introduced, 61 after. Patients were classified as either malnourished or well-nourished. "Nutritional status did not differ significantly at admission but was worse at surgery after the introduction of DRGs," and malnourished patients had more complications under DRGs, say the authors. They suggest finding other ways to treat these malnourished patients, perhaps adjusting DRG payments or providing preadmission nutritional support.

JAMA July 22, 1988

ORAL STEROIDS FOR ASTHMA

High-dose oral corticosteroids can be as effective in treating asthma as those administered intravenously, finds a report in JAMA. The study, by David Ratto, MD, of the Los Angeles County-University of Southern California Medical Center, Los Angeles, involved 77 asthma patients who received methylprednisolone either in high oral doses or intravenously. There were no differences between the groups in measures of respiratory function, days hospitalized, or side effects, say the authors. "We conclude that oral methylprednisolone is safe and effective in the treatment of status asthmaticus," they write. Commenting editorially, Roger C. Bone, MD, of Rush-Presbyterian-St. Luke's Medical Center, Chicago, suggests a "step care" approach to asthma, selecting treatment agents of increasing power depending upon effectiveness for specific symptoms.

JAMA July 22, 1988

MOTION SICKNESS MEDICINE CAUTION

It is well-known that anticholinergic drugs, used to control vertigo and vomiting, can interfere with memory, cognition and orientation, especially in the elderly. Now, a letter in JAMA suggests these problems can result even when low doses of such drugs are used, as in transdermal patches used to control motion sickness. Renzo Rozzini, MD, of the St. Orsola Hospital-FBF, Brescia, Italy, and colleagues describe a 77-year-old woman hospitalized for sudden memory loss and disorientation after a trip to a resort. No abnormalities were found and she was released when her symptoms resolved, but the problems recurred when she returned home after her vacation. This time doctors learned that the woman used a transdermal scopolamine patch to prevent car sickness on her way to and from the resort. "The appearance of delirium requires a complete assessment of the patient to detect reversible conditions such as that reported here," the authors write.

CORONARY BYPASS SURGERY MAY OFTEN BE PERFORMED INAPPROPRIATELY: STUDY

Significant numbers of coronary artery bypass operations are being performed for inappropriate reasons, suggests, a report in JAMA.

Only 56 percent of bypass operations performed in three randomly chosen hospitals in a western state were performed for appropriate reasons, say authors Constance Monroe Winslow, MD, of the University of California-Los Angeles Center for the Health Sciences, and colleagues. In a random sampling of 386 bypass operations performed in these hospitals during 1979,

1980, and 1982, 14 percent were performed for inappropriate and 30 percent for equivocal reasons. The percentage of appropriate surgeries varied by hospitals, from 37 to 78 percent.

The appropriateness of bypass surgery was determined using a system designed for the RAND Corp-UCLA Health Services Utilization Study, the authors report. Based on a literature review and consultation with cardiac experts, a list of 488 possible indications for performing bypass surgery was prepared. A panel of physicians rated the appropriateness of each indication on a nine-point scale. The authors assigned one of the 488 indications to each of the 386 bypass recipients based on their hospital records.

Twenty-eight percent of the appropriate cases (16 percent of the total) involved either left main-vessel disease, or three-vessel disease and either unstable angina or stable angina on maximal medical therapy. The most common example of inappropriate surgery (2 percent of the total) was the performance of a bypass within 24 hours of admission for unstable angina, without adequate trial of medical therapy, when angiography showed only two clogged vessels. The data provided an opportunity to compare the appropriateness of bypass surgery in patients younger or older than age 65, the authors say. "There is public concern because of the availability of the Medicare insurance program that the elderly may be receiving a greater number of inappropriate procedures than their younger counterparts. The data do not support this concern. If anything, the elderly might have received slightly more appropriate care."

Although representative of patients undergoing bypass surgery in western states, the authors point out that "further work is needed to generalize these results to the rest of the United States." However, their findings can be used to "highlight the gray areas in our understanding of a procedure's use and to direct the focus of future randomized trials of its efficacy."

While clinicians may disagree on whether bypass surgery should be performed on patients for indications with equivocal ratings, few would argue that the services should go first to all patients with clearly appropriate reasons for their use, they say. "When confronted with scarce resources, planners may wish to use this type of information to help make difficult allocation decisions."

In an accompanying editorial, Albert G. Mulley, Jr. MD, MPP, and Kim A. Eagle, MD, of the Massachusetts General Hospital and Harvard Medical School, Boston, note that the rating panel agreed on only 42 percent of the surgical indications. In addition, appropriateness ratings from a panel in Great Britain applied to similar data finds a far higher rate of inappropriate surgeries. This disagreement can be explained by the uncertainty associated with untested theory, and should temper doctrinaire approaches to clinical problems, they write. "Policymakers should resist the temptation to use appropriateness ratings as a quick fix."

While such ratings may allow targeting of extreme practices for more extensive prospective review, "there is a real risk of codifying indications that are seemingly objective or easily abstracted but not based on adequately tested current theory... The real need is for more

information about the outcomes of medical practices. The investment of dollars to reduce uncertainties that underline practice variation should be a national priority," the editorial says.

Appropriate care for patients "often depends on their attitudes toward risk and what they value. There are legitimate reasons why society may constrain choice by determining what it will allow or pay for, but there is great latitude for personal definition of what is worthwhile. Patient's best safeguard against inappropriate care is involvement in a decision-making process that allows communication of their attitudes and values," they conclude.

JAMA July 22, 1988

NEW RAPID HIV TEST HOLDS PROMISE FOR THIRD WORLD: STUDY

A new, rapid, inexpensive test may help developing countries prevent the spread of human immunodeficiency virus (HIV) infection through blood transfusions, says a report in *JAMA*.

The test for HIV antibodies in blood serum also may be useful in other clinical settings where prompt testing and counseling is needed, say the study's authors, Thomas C. Quinn, MD, of the National Institutes of Health, Bethesda, Md., and the Johns Hopkins University School of Medicine, Baltimore, and colleagues.

However, in an accompanying editorial, William L. Heyward, MD, MPH, and James W. Curran, MD, MPH, of the Centers for Disease Control, Atlanta, report that a recent study shows the test's performance in the field is not quite as good as it is in the research environment. They also caution against regarding the test as "diagnostic," without confirming testing and follow-up, and raise concerns about its use by the public in a home setting or elsewhere.

The rapid latex agglutination slide test, which is not yet licensed by the Food and Drug Administration, is as sensitive and specific as the two most often used tests for HIV infection, the ELISA and Western blot assay, the authors say. Unlike those tests, however, the latex agglutination assay yields results in a few minutes instead of hours, is simple to learn and perform, and is stable at room temperature. These advantages should allow it to be used in developing areas of the world, where, due to severely limited resources, blood for transfusions is not screened, the report says.

In areas of Africa, HIV infection is endemic and the need for transfusions is high due to anemia caused by malaria, malnutrition, and other diseases. Many areas have no blood banks; instead, blood donated by friends or relatives of the patient is transfused within an hour of collection. Transfusions have become a major means of HIV transmission in these areas; in one Zaire hospital alone, an estimated 1,800 persons a year may become infected through blood transfusions, the authors report.

The new test uses minute latex beads coated with pieces of a protein, or polypeptide, found in the envelope of the

AIDS virus. These protein pieces are produced by bacteria in which recombinant DNA derived from the virus has been inserted. Unless recently exposed, HIV-infected persons almost always have antibodies to the HIV envelope protein in their blood. To determine if a person has been infected, a sample of his or her blood serum is mixed with a suspension of coated latex beads. If antibodies are present, they will attach to the polypeptide coating and the beads will clump. By comparing the clumping effects of the serum sample with control samples, trained technicians can quickly determine whether the blood is infected, the authors say.

The authors compared the results of the new test with that of the ELISA and Western blot assay for 2,820 serum samples from blood donors and patients from diverse geographical regions, including 1,600 donors from a hospital in Zaire. The latex agglutination test proved as reliable as the Western blot in populations with a relatively high prevalence of infection, they report. In an analysis using a reference panel of 1,220 serum samples from patients around the world, the new test was highly sensitive (99.3 percent) and specific (100 percent) compared with Western blot, regardless of the patients' geographic origin or clinical phase of infection. "However, additional testing in populations with low prevalence is urgently required to better determine the specificity and predictive value of the test in those populations," the authors caution.

In their editorial, Hayward and Curran say recent use of the new test in a Zaire hospital under real conditions has produced less impressive results of 71.4 percent sensitivity and 93.7 percent specificity, meaning significant amounts of infected blood was not being detected. "These results confirm the need for further comparative evaluation and quality control of laboratory performance of these assays under field conditions," they write. "The needs for technician proficiency and expertise in test interpretation raise concerns about the use of tests by the general public in the home setting or elsewhere."

They agree with the authors that rapid tests may also be useful in developed countries in clinical settings where patient compliance in return visits is poor—such as emergency departments and sexually transmitted disease and drug abuse clinics. Quick return of test results would allow immediate counseling and implementation of other prevention and control measures, the authors say. For example, they cite the Baltimore City Health Department's Anonymous Counseling and Testing Site, where in 1986 only 54.8 percent of the 306 HIV-seropositive individuals returned for test results and counseling.

The latex test was developed by Cambridge BioScience Corp., Hopkinton, Mass. Except for one author, who is a company employee, no other author has any financial interest in the company.

JAMA July 22, 1988

VITAMIN E AND POST-RHINOPLASTY NOSEBLEEDS

Rhinoplasty patients should not take vitamin E before surgery, as it might play a role in postoperative bleeding,

says a report in July's *Archives of Otolaryngology-Head and Neck Surgery*. Authors Michael M. Churukrian, MD, of the University of Southern California School of Medicine, Los Angeles, and colleagues say two patients they treated for postrhinoplasty nosebleeds both were taking "megadoses" of vitamin E. Sixteen of 100 other control patients with uncomplicated rhinoplasties also were taking vitamin E, but at lower doses. The authors say a literature review found "recent evidence demonstrating a marked decrease in platelet adhesiveness with megadose ingestion of vitamin E." As a result, even though cause-and-effect can't yet be shown, the evidence suggests vitamin E "is contraindicated in the presurgical patient," they say. "Because of the long half-life of this fat-soluble vitamin, patients should abstain from usage for at least two weeks preoperatively."

PEDIATRICIANS UNDER-REPORTING OF PSYCHIATRIC PROBLEMS IN CHILDREN

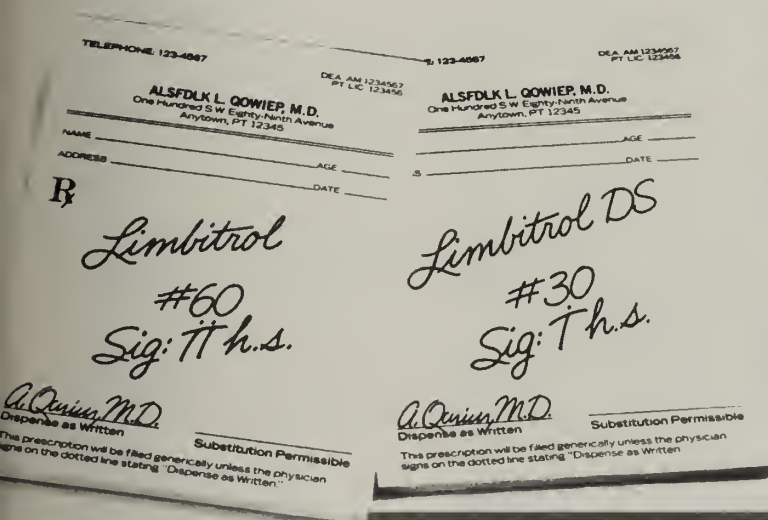
Pediatricians tend to under-report both minor and serious psychiatric problems in the children and adolescents they see, a report in July's *American Journal of Diseases of Children (AJDC)* says. Authors Grace Chang, MD, of the Yale University School of Medicine, New Haven, Conn., and colleagues studied reports by 35 physicians on psychiatric problems in 85 patients aged 6 to 17. These were compared with reports from the children and their parents as derived from direct, independent assessments, as well as with reports by a child psychiatrist who used all available data on the children. The authors found poor agreement between the physician assessments and reports from all three other sources. Physicians tended to underreport both minor and serious psychiatric problems. "These findings suggest that additional training in the detection of psychiatric problems for nonpsychiatric physicians is necessary," says the study.

WRITING TEST CORRELATES WITH DEMENTIA SEVERITY IN ALZHEIMER'S

An analysis of writing proficiency seems to be a simple way of assessing the severity of dementia caused by Alzheimer's disease, a report in July's *Archives of Neurology* says. The study, by Jennifer Horner, PhD, of the Duke University Medical Center, Durham, NC, and colleagues, looked at the impairment of writing ability in 20 patients with mild to moderate dementia caused by early-onset Alzheimer's. The patients were shown a picture and asked to describe in writing what they saw. Their writing proficiency was compared with results of standard tests of cognitive function and ratings of the degree of their dementia. "In these patients, significant correlations were observed between this brief test of narrative writing ability and the severity of dementia," the authors say. "We suggest that a sample of narrative writing should be included in the neuropsychological evaluation of Alzheimer's disease."

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References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Feighner VP, et al: *Psychopharmacology* 61:217-225, Mar 22, 1979.

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Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants; concomitant use with MAOIs or within 14 days of monoamine oxidase inhibitors (then initiate cautiously, gradually increasing dosage until optimal response is achieved); during acute recovery phase following myocardial infarction.

Warnings: Use with caution in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur when used with anticholinergics. Closely supervise cardiovascular patients. Arrhythmias, sinus tachycardia, prolongation of conduction time, myocardial infarction and stroke reported with tricyclic antidepressants, especially in high doses. Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

Adverse reactions not reported with Limbitrol but reported with one or both components or closely related drugs: **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, increased or decreased libido. **Neurologic:** Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns. **Anticholinergic:** Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract. **Allergic:** Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus. **Hematologic:** Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue. **Endocrine:** Testicular swelling, gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion. **Other:** Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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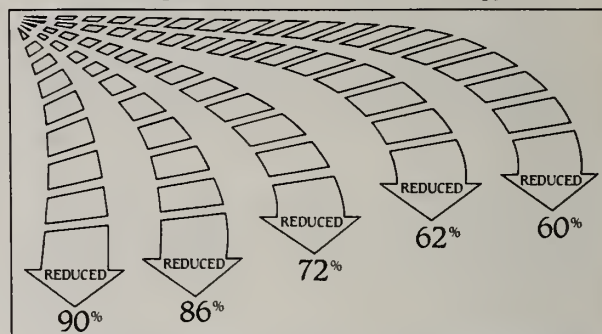
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BOLETIN

VOL.80 - NUM. 10

OCTUBRE 1988

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Sr. Rubén D'Acosta, Director Ejecutivo
 Asociación Médica de Puerto Rico
 Apartado 9387, Santurce, P.R. 00908

Publicación mensual, \$40.00 anuales. El Boletín se distribuye a todos los miembros de la Asociación Médica de Puerto Rico como parte de su cuota anual.

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Boletín de la Asociación Médica de Puerto Rico is published monthly for \$40.00 per year by Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, Santurce, P.R. 00908.

"POSTMASTER" Send address changes to Boletín Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, Santurce, P.R. 00908.

Second Class postage paid at San Juan, P.R.

USPS-060000

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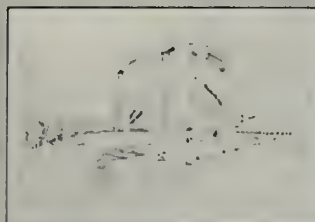
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BOLETIN



VOL. 80 / NUM. 10

OCTUBRE 1988

NUESTRA PORTADA

Instituto de Cardiología San Pablo. Boceto arquitectónico de las facilidades del instituto. Este instituto forma parte del Centro Médico San Pablo, un complejo de facilidades hospitalarias y ambulatorias privadas que ofrecen servicios médicos a gran parte de la región norte y central del país.

El Instituto Cardiovascular es la más reciente adición a este Centro Médico con afiliación a dos escuelas de medicina.

Este boceto arquitectónico complementa la portada de octubre pasado donde se hizo la primera presentación del Centro Médico San Pablo.

EDITORIAL



Celebramos con este número del Boletín de la Asociación Médica de Puerto Rico el Duodécimo Aniversario del Hospital San Pablo y el inicio del primer año de operaciones del Instituto de Cardiología San Pablo.

Nos llena de regocijo la respuesta extraordinaria de la facultad de nuestro Centro Médico, quienes sometieron un número considerable de artículos para publicación.

Desafortunadamente, debido a limitaciones de espacio, nos vemos obligados a solamente publicar solo algunos de ellos, los restantes serán sometidos para publicación en un futuro cercano.

Este segundo número del Boletín de la AMPR, donde los autores son miembros de la Facultad del Hospital San Pablo recoge una gran variedad de experiencias clínicas y revisiones de la literatura con materia relevante al funcionamiento de nuestro Centro. Se incluyen también artículos sobre la problemática cardiovascular, que servirá como marco de referencia para las futuras gestiones profesionales y clínicas del Instituto Cardiovascular San Pablo.

Agradezco la gentil invitación de la Junta Editora del Boletín de la Asociación Médica de Puerto Rico de regresar como editor invitado de este número.

Quiero a través de este Editorial expresar mi agradecimiento por la ayuda y asesoría valiosa que nos ofreció el doctor Villavicencio, Presidente de la Junta Editora del Boletín.

Felicitamos a la Junta Editora del Boletín en su deseo de continuar desarrollando este tipo de actividad científica entre las diferentes facultades de los hospitales de Puerto Rico.

Pedro M. Mayol, MD
Sub Director Médico,
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Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (penicillinase and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, and *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri*, and *Shigella sonnei** when antibacterial therapy is indicated.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with Cipro[®] may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN SHOULD NOT BE USED IN CHILDREN OR PREGNANT WOMEN. The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and norfloxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

General

As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and very rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals. Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded. Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

Drug Interactions

Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin, resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

Probenecid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients

Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum concomitantly or within two hours after dosing. Ciprofloxacin may cause dizziness or lightheadedness; therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

- Salmonella/Microsome Test (Negative)
- E. coli* DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V₇₉ Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- Saccharomyces cerevisiae* Point Mutation Assay (Negative)
- Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the following three *in vivo* test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Microsome Test (Mice)
- Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in animals have not yet been completed.

Pregnancy—Pregnancy Category C

Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in

CONVENIENT B.I.D. DOSAGE

Recommended dosage schedule

Infection Site*	Severity of Infection	Dosage
Respiratory Tract* Bone and Joint*	Mild/Moderate	500 mg B.I.
Skin/Skin Structure*	Severe/Complicated	750 mg B.I.
Urinary Tract*	Mild/Moderate	250 mg B.I.
	Severe/Complicated	500 mg B.I.
Infectious Diarrhea*	Mild/Moderate/Severe	500 mg B.I.

pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers

It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Ciprofloxacin should not be used in children because it causes arthropathy in immature animals (WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, pooled in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%).

The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%), vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and rash (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below. Those type quinolones are italicized.

GASTROINTESTINAL: (See above), painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM: (See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.

SKIN/HYPERSENSITIVITY: (See above), pruritus, urticaria, photosensitivity, flushing, fever, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

SPECIAL SENSES: blurred vision, disturbed vision, (change in color perception, overbrightness of light), decreased visual acuity, diplopia, eye pain, tinnitus, bad taste.

MUSCULOSKELETAL: joint or back pain, joint stiffness, achiness, neck or chest pain, flare-up of gout.

RENAL/UROGENITAL: interstitial nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR: palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY: epistaxis, laryngeal or pulmonary edema, hiccup, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to relationship:

Hepatic—Elevations of: ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LOH (serum bilirubin) (0.3%).

Hematologic—eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated platelets (0.1%), pancytopenia (0.1%).

Renal—Elevations of: Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: Elevation of serum gamma-glutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, a bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. In the event of serious toxic reactions from overdosage, hemodialysis or peritoneal dialysis may aid in the removal of ciprofloxacin from the body, particularly if renal function is compromised.

DOOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

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* Due to susceptible strains of indicated pathogens. See indicated organisms in Brief Summary.

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CLINICAL STUDIES

Retrograde Coronary Sinus Cardioplegia in Patients with Severe Ventricular Dysfunction

Manuel J. Martínez, MD, FACS
Raúl García Rinaldi, MD, FACS

Abstract: A technique for infusion of cardioplegia via the coronary sinus is described. To demonstrate its simplicity, potential benefits and capability of protecting the myocardium; we present our initial experience in 13 consecutive patients with severe left ventricular dysfunction and total occlusion of 2 of its coronary arterial systems. All patients were initial survivors and were removed from cardiopulmonary bypass with cardiac index of at least 2.0L/Min/M². The initial experience seems to support our intent for continued use of retrograde coronary sinus cardioplegia (RCSC).

The re-introduction of hypothermic potassium cardioplegia following the studies of Kirsh, Hearse, Gay and Ebert is in a large measure responsible for the excellent results attainable in cardiac surgery today.¹⁻³ However, intraoperative myocardial damage still occurs due to inadequate preservation.⁴ One of the causes is the uneven distribution of cardioplegia in areas supplied by obstructed vessels.⁵ Many strategies have been developed to remedy this situation. The one most recently employed is the retrograde infusion of cardioplegia through the coronary sinus. Although its feasibility and safety has been shown,⁶⁻⁸ surgeons are reluctant to use it, perhaps because some may find it cumbersome and others are unaware of its potential benefits.

We utilize a simple and effective method for delivery of cardioplegia through the coronary sinus. Its effectiveness in preserving myocardium was evident in 13 consecutive patients with occlusion of two or more its major coronary systems and severe left ventricular dysfunctions. All patients survived operation and only 4 required temporary support circulatory assistance with an intra-aortic balloon pump.

Methods

Cardiopulmonary bypass is instituted using bicaval and aortic cannulation as previously described.⁹ Systemic hypothermia to 28°C is used and the heart is arrested by infusing 750 ml of crystalloid potassium cardioplegia through the aortic root after aortic cross clamping. Cold

(4°C) normal saline is applied topically. The caval tapes are snared and a small atriotomy is made low in the right atrium (Fig. 1). The tip of a 12 Fr. Foley catheter is introduced in the coronary sinus and the balloon inflated gradually with saline solution until it fits snugly at the rim. The balloon is positioned so that approximately one half of its circumference protrudes into the atrium to avoid blocking the lesser cardiac vein or other right ventricular venous drainage. The cardioplegia infusion line from the pump is routed to the Foley catheter by repositioning the clamp on a "Y" connector which has been spliced on the main cardioplegia line. A roller pump is used to infuse the cardioplegic solution at a constant rate; infusion pressure is constantly monitored and not allowed to exceed 50 mm Hg. Venting is done through the aortic root utilizing the same needle that had been used for the initial bolus. If more that two liters of cardioplegia is used, a hemoconcentrator is added to the cardiopulmonary bypass system.

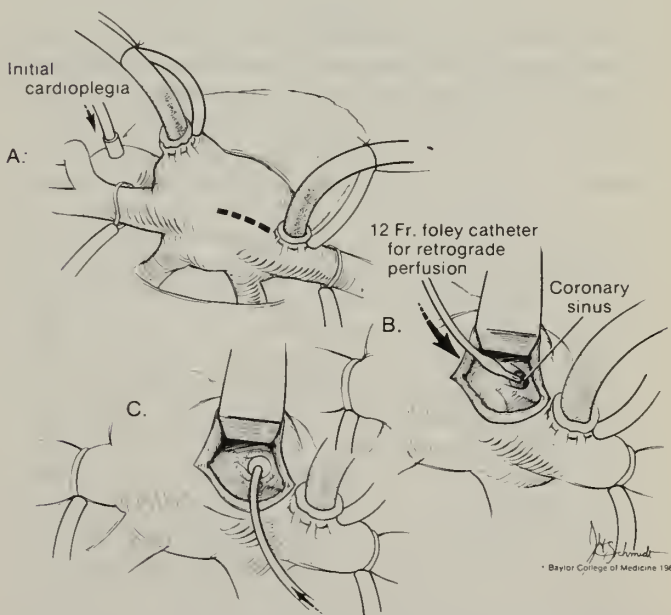


Figure 1: The technique for delivery of cardioplegia through the coronary sinus. Note: A. Initial bolus of cardioplegia into the aortic root and the placement of the incision; B. Introduction of a 12 Fr. Foley catheter in the coronary sinus; and C. The balloon is inflated to fit at the rim with one half of the circumference protruding.

The infusion is detained and systemic warming is started when the last distal anastomosis is begun or after the valve is seated and sutures tied when concomitant aortic or mitral valve replacement is done. The aorta is unclamped after completion of all distal anastomoses and when the aorta or left atrium are closed and the catheter removed from the coronary sinus. The atriotomy is closed in two layers with 4.0; polypropylene and caval tapes are then loosened. The operation is completed and the patient weaned from cardiopulmonary bypass.

Results

Our experience is summarized in Table I.

The following three patients exemplify the potential benefit of coronary sinus cardioplegia in patients with poor ventricular function and total occlusion of 2 coronary systems.

Patient 1: A 60 year-old diabetic male presented with a one-hour history of crushing chest pain. He was cold with evidence of poor peripheral perfusion. The systolic blood pressure was 80 mm Hg, pulse 100 beats per minute and fine rales were heard over both lower lung fields.

The ECG demonstrated an old extensive inferior myocardial infarction and an acute antero-septal myocardial infarction in evolution. Immediate cardiac catheterization and coronary angiography was done because of his compromised hemodynamic state. The pulmonary artery pressure was 44/30 mm Hg with a capillary wedge pressure of 33 mm Hg. There was occlusion of the left anterior descending (LAD) without collateral filling and occlusion

of proximal right coronary artery (RCA) which filled by ipsilateral collaterals. The circumflex system was small (Fig. 2)



Figure 2. Left Anterior oblique view of left coronary artery infection in patient 1. Note: Totally occluded proximal left anterior descending; the small circumflex coronary artery is the only patent system.

A percutaneous intra-aortic balloon pump (IABP) was inserted via the right common femoral artery in the catheterization laboratory. Coronary artery bypasses using saphenous vein were done to the LAD, obtuse marginal branch of the circumflex coronary artery (CCA) and distal RCA utilizing retrograde coronary sinus cardioplegia (RCSC).

The patient was weaned from cardiopulmonary bypass without difficulty with the IABP. On the second postoperative day the IABP was removed and he was extubated shortly thereafter. He was discharged on the tenth postoperative day.

Patient 2: A 61 year-old diabetic was referred for myocardial revascularization. Two years previously he had sustained an extensive inferior wall myocardial infarction and suffered from stable angina until 2 months prior to admission. Since then the frequency of angina had increased, and on two occasions he had been admitted to the hospital with angina and congestive heart failure. A resting gated scan revealed an ejection fraction of 22%.

Because of continued disabling angina in spite of aggressive medical management, cardiac catheterization and coronary angiography were performed. The angiography ejection fraction was 20% and the left ventricular end diastolic pressure (LVEDP) was 25 mm Hg. The left coronary system was dominant and the CCA was occluded. The LAD had a 95% stenosis proximally and the RCA gave branches only to the right ventricle. (Fig. 3)

Table I

Clinical Experience with Retrograde Coronary Sinus Cardioplegia Function and in Patients with Poor LV Function and Occlusion of Two Coronary Arterial Systems

Patient	Procedure	E.F.	Inotropic Support (Duration)	IABP
1	CABG X6	20%	None	NO
2	CABG X4	20%	Dopamine (8 hours)	NO
3	CABGX4, LVA	30%	Dopamine (8 hours)	NO
4	CABG X6, LVA	25%	None	NO
5	CABG X3	30%	None	NO
6	CABG X4	26%	Dopamine (48 hours)	YES
7	CABG X4, LVA	30%	Dopamine (72 hours)	YES
8	CABG X3, AVR	20%	None	NO
9	CABG X3	28%	Dopamine (72 hours)	NO
10	CABG X3, AVR	30%	None	NO
11	Re-do	25%	None	NO
	CABG X3, LVA			
12	CABG X5, Cholecystectomy	26%	Dopamine (48 hours)	YES
13	CABG X3, LVA	25%	Dopamine (48 hours)	YES

CABG: Coronary artery bypass grafting

AVR: Aortic valve replacement

LVA: Left ventricular aneurysmectomy

E.F.: Ejection fraction

IABP: Intra aortic balloon pump



Figure 3. Right anterior oblique view of left coronary injection in patient #2. Note totally occluded CCA and 95% stenosis of LAD. A small RCA was also totally occluded.

Saphenous vein coronary bypass operations to the LAD, first diagonal, obtuse marginal branches 1 and 2, were performed utilizing RCSC. The patient was weaned from cardiopulmonary bypass without inotropic support. He had an uneventful convalescence and was discharged on the tenth postoperative day.

Patient 3. A 77 year-old male with history of two previous myocardial infarctions was admitted with unstable angina pectoris. To delineate his coronary anatomy, cardiac catheterization and coronary angiography was undertaken. The ejection fraction was 24% and the cardiac output of 3.07 l/min. The CCA and RCA were occluded and the LAD had a 75% stenosis. Because of advanced age, aggressive medical therapy was recommended by his cardiologist. However, his angina worsened and six vessel coronary artery bypass procedures were performed using RCSC. The patient was weaned from cardiopulmonary bypass without inotropic support. He was extubated on the first postoperative day and the convalescence was uneventful. He was discharged 11 days after surgery.

We have used RCSC in 13 patients with severe left ventricular dysfunction (ejection fraction less than 30%, average = 26% and occlusion of at least two coronary arterial trunks. Eight patients required additional procedures: 5 a left ventricular aneurysmectomy, 2 aortic valve replacement and one cholecystectomy. All patients survived the operation. One patient developed ventricular fibrillation on the 8th postoperative day. Although he survived this event he expired 2 weeks later as a result of pneumonia. One patient died 4 months after surgery due to ventricular fibrillation. The remaining 11 patients are alive and well from 2 to 15 months after surgery.

There were no instances of coronary sinus trauma. The right atriotomy and bicaval cannulation did not pose morbidity in any of the patients. Several patients required

atrioventricular sequential pacing, but none beyond the first 2 hours postoperatively. Prolonged asystole was not encountered. All patients were weaned from cardiopulmonary bypass with cardiac index better than 2.0 l/min/M² although 4 required IABP support (one inserted before surgery) and 7 inotropic drugs.

Discussion

The valveless nature of the coronary circulation and the intramural connections between arteries, veins and cardiac chambers were described by Pratt in 1898 and confirmed by Wear in 1928.^{10, 11, 12} Their observations and those of others clearly demonstrated a myocardial capillary bed interconnecting directly with the coronary arteries, arterioles, and to the coronary sinus via venules and veins. Connections to cardiac chambers were also demonstrated via arterio-sinusoidal vessels, myocardial sinusoids, thebesian veins and arterio-luminal vessels; thereby, creating a rich myocardial vascular bed where blood could flow in either direction unobstructed.¹³

Based on these observations and Beck's results with aorto-coronary sinus anastomoses using vein grafts or the left subclavian artery,⁴ Blanco and colleagues maintained the heart beating in dogs whose aorta was crossclamped and opened. The myocardium was perfused via the coronary sinus utilizing crossed circulation.¹⁵ Lillehei pioneered this technique clinically in 1956 in patients with aortic stenosis utilizing the newly developed pump oxygenator, with excellent results.¹⁶

In spite of the encouraging early results, the clinical use of retrograde coronary sinus perfusion lay dormant in clinical practice. This was in part due to the advent of antegrade coronary perfusion with coronary cannulae and the acceptance of cardioplegia given through the aortic root. However, the concept of using the coronary sinus for myocardial protection has recently been reintroduced, this time by infusing cardioplegia. It has now been shown to achieve evenly distributed myocardial hypothermia and to abolish temperature gradients between areas, in the presence of coronary artery occlusion.^{8, 17} Furthermore, Saylam found a uniform myocardial distribution of India ink when injected through the coronary sinus and Bolling demonstrated equally distributed staining of the right and left ventricle, when methylene blue is infused retrogradely.^{7, 8} These experimental results are indications of uniform distribution of infusate throughout the myocardium including the right ventricle when the coronary sinus is utilized.

The administration of cardioplegia through the coronary sinus in the clinical setting has initially gained more acceptance in Europe than in this country. Menasche found RCSC as effective as antegrade delivery in 12 patients undergoing aortic valve replacement. Their postoperative hemodynamic parameters were the same as those obtained when antegrade coronary cardioplegia was used.⁶ Other European reports have found superior results in patients with critical coronary artery stenosis and advocate its routine use for myocardial revascularization.¹⁷ In this country; however, the acceptance of retrograde coronary sinus perfusion has been slower.

We believe the technique we employ is simple and efficacious in preserving the myocardium. Our initial experience in a sub-group of patients with severely impaired left ventricular function (ejection fraction less than 30%) and proximal occlusion of at least two of the main coronary arterial trunks has been rewarding. The technique is similar to that described by Menasche⁶ with two exceptions: First, we give an initial bolus of cardioplegia via the aortic root to accomplish asystole and initial myocardial hypothermia and, second, the continuous infusion of cardioplegia throughout the entire procedure, rather than reinfusions at intervals. The aortic root infusion prevents a prolonged period of ventricular fibrillation which may be deleterious to the already ischemic myocardium, by depletion of its energy stores. In addition, it allows the surgeon to precisely position the perfusion catheter in the coronary sinus without haste and thus prevent injury to this delicate structure.

The infusion of cardioplegia given at constant rate maintains the temperature constant between 7-14 C throughout the procedure. Furthermore, better protection of the posterior ventricular free wall may be accomplished by using RCSC in combination with antegrade cardioplegia as suggested by Shiki.¹⁸

Our initial experience with RCSC in these difficult patients is rewarding. All 13 patients survived operation and showed a stable hemodynamic state following the procedure. These initial results are suggestive that RCSC can achieve satisfactory myocardial preservation in patients with impaired ventricular function and occlusion of at least two coronary arterial systems and in fact, it may be the best choice.

Other advantages of RCSC previously outlined included prevention of injury and late stenosis of the coronary ostia during AVR, even cooling of the myocardium in the presence of coronary occlusion, and expeditious performance of the surgical procedure without interruption.^{6, 7}

Mortality rates of up to 37% have been reported in patients with poor left ventricular function;¹⁹ and total occlusion of two of the three main trunks is likely to increase operative risk even more. To our knowledge this is the first report of RCSC used in a selected group of high risk patients in this country. Since mortality is a definite end point not subject to argument, our results using RCSC in this high risk group of patients is an improvement upon that of previously reported series. Thus, our intent to continue its use.

Resumen: Se describe el procedimiento modificado de cardioplejía retrógrada del seno coronario y la experiencia inicial con trece enfermos afectados por disfunción ventricular izquierda severa y oclusión total de dos de sus sistemas coronarios. Todos sobrevivieron inicialmente. El procedimiento es sencillo y esta experiencia inicial apoya nuestra intención de continuar empleándolo en estos casos.

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A New Method for Estimating the Radioactive Iodine Dose in the Treatment of Hyperthyroidism

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Abstract: We present our preliminary experience with a new method for estimating the radioactive iodine (I^{131}) dose for the treatment of thyrotoxicosis utilizing a fixed dose of the isotope per calculated thyroid gland volumen. Nineteen patients (16 females and 3 males) with Graves' disease were treated using the experimental protocol. The calculated I^{131} dose ranged from 2.6 to 14.5 millicuries (mCi) for an average dose of 7.6 mCi. At one year, 63% of the patients were euthyroid and 21% hypothyroid. The patients were followed for three years and our results are compared with those of other studies reported in the world literature.

The physiologic basis for radiiodine therapy in the treatment of hyperthyroidism lies in the exceptional concentration of iodine achieved by the thyroid gland and in the radiation-induced cell damage that gradually occurs after exposure to the isotope.¹ However, the effectiveness of a particular dose depends upon several factors that include iodine uptake, gland size, the effective half life of iodine in the gland, tissue distribution and the radiosensitivity of the follicular cells.¹ Since some of these factors can't be easily evaluated, practitioners have devised different methods in trying to deliver a curative dose with a low incidence of hypothyroidism.

The most common strategies that have been applied so far include: The "fixed-dose method", the "microcurie per gram method" and the "delivered rads methods".² As its name implies, in the first modality a fixed dose of 3 to 5 millicuries (mCi) of radioactive iodine (I^{131}) is given orally to patients regardless of gland size, uptake or severity of disease. Sometimes, larger or variable doses are used based on the physician's past experience with a specific population.²

The "microcurie per gram method" utilizes a fixed dose of I^{131} per subjective estimation of gland size divided by the 24-hour iodine uptake.¹ Finally, the "delivered rads method" uses the Quimby - Marinelli - formula³ for calculating the therapeutic dose:

$$\text{Dose in microcurie (uCi)} = \frac{(100) \text{ Rads selected} \times \text{estimated gland weight}}{\% \text{ uptake at hours} \times 90}$$

One of major flaws of these approaches resides in the fact that there is little sensitivity in the conventional way of estimating gland size (usually done by external palpation).

Brown and Spencer threw some light into this problem when in 1978 they reported a very close correlation between volumetric measurement of thyroid glands in autopsy specimens and their estimated volumes by using a standard geometric formula for calculating the volume of an ovoid.⁴ In this formula, volume $V = \pi / 6 \times a \times b \times c$ where the letters represent height, width and thickness respectively. A combination of scintiscan and ultrasonogram was used for calculating the parameters a, b and c.

In this paper we present a new method for estimating the radioactive iodine dose for thyrotoxic patients using a fixed dose of I^{131} per volume of thyroid gland as calculated by Brown and Spencer's formula. We compare our results with the outcome of patients treated in the past by conventional non-standardized doses at our institution.

Materials and Methods

Nineteen patients (16 females and 3 males) whose ages ranged from 21 to 65 years, with clinical and laboratory findings compatible with thyrotoxicosis were selected to enter our study. Failure to control their condition with conventional oral antithyroid medications for over a year characterized all patients.

After entering the protocol all antithyroid medications (except for beta blockers) were discontinued for at least two weeks. Continued beta blocker treatment assured cardioprotection for the entire length of the study. Thyroid scans and ultrasonograms were performed in all subjects. Volumetric (V) calculations of the glands were performed after the formula $V = \pi / 6 \times a \times b \times c$.

Height (a) was measured using the scintiscan image, while width and thickness (b, c) were measured by the sonographic technique. A fixed dose of 200 uCi of I^{131} per cubic centimeter of gland volume was given to each patient.

The subjects were followed at monthly intervals for an average of three years. Clinical evaluations and measurements of thyroid function tests (T4, TSH by radioimmunoassay, T3 by resin uptake) were used to assess the patients' metabolic status.

Results

The calculated iodine dose delivered to our patients ranged from 2.6 to 14.5 mCi. The average dose was 7.6 mCi (Table I).

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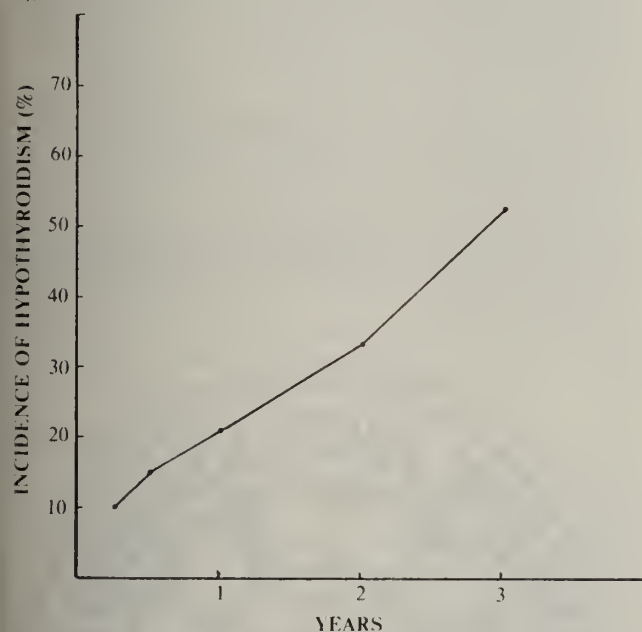
This study was presented at the 1987 meeting of the "Sociedad Puertorriqueña de Endocrinología y Diabetología".

Table I

Patient	Last Treatment Date	Total Dose (mCi)	Time Patient Became Euthyroid	Actual Condition
ITA	Oct. 1985	8	1 year - 10 mo.	Euthyroid
ATS	Oct. 1982	4.2	2 years - 7 mo.	Hypothyroid
SFS	May. 1984	9.5	—	Hyperthyroid
ADC	Feb. 1985	6	1 year - 3 mo.	Euthyroid
CDP	Oct. 1984	4.8	4 months	Euthyroid
FCR	Jun. 1985	17	2 years - 2 mo.	Euthyroid
RCR	Mar. 1984	10	1 year	Hypothyroid
ZAB	Nov. 1983	6.8	8 months	Hypothyroid
CEC	Oct. 1984	2.6	4 months	Euthyroid
MJC	Mar. 1984	5.77	11 months	Hypothyroid
GMM	Jun. 1984	4.2	2 years - 4 mo.	Hypothyroid
HPF	May. 1984	8	1 months	Hypothyroid
CPP	May. 1986	6	—	Hyperthyroid
IRR	May. 1984	6.1	2 months	Hypothyroid
MRF	Feb. 1985	4.6	1 year - 2 mo.	Euthyroid
CRG	Feb. 1985	7	3 months	Hypothyroid
MSV	May. 1984	14.5	6 months	Hypothyroid
ERJ	Sep. 1986	9.6	—	Hyperthyroid
SLA	Nov. 1983	10.9	2 months	Hypothyroid

Out of nineteen patients entered in the study, twelve (63%) were euthyroid, four (21%) hypothyroid and three (16%) remained hyperthyroid at the end of one year. From the first year on, the incidence of hypothyroidism rose steadily up to 53% at the end of three years of average follow-up-time (Figure 1).

Figure 1



Cummulative incidence of hypothyroidism following I^{131} treatment estimated by volumetric method

Discussion

The objective of radioactive iodine treatment in hyperthyroidism is to render the patient euthyroid with a single dose, if possible, in a reasonable amount of time. The extent to which this goal is achieved depends, as mentioned earlier, upon several factors, but the most determining ones are: the administered dose and the patient's sensitivity.¹

The "dose factor" is well illustrated in several classic reports. Rapoport et al.⁵ found that low I^{131} doses (80 uCi/gram) induced a 39% rate of euthyroidism within one year while Barzelatto, using intermediate doses (160 uCi/g), rendered 62% of his patients euthyroid in the same period of time.⁶ At the other side of the spectrum, Safa and Skillern achieved a 90% euthyroidism rate using high doses (160-240 uCi/gram).⁷ As expected, the incidence of hypothyroidism was very high in the latter study, thus verifying the old dictum: the higher the dose, the sooner the cure, the higher the incidence of hypothyroidism.

In our study we found that using volumetric calculations for delivering radioiodine resulted in an average dose of 7.6 mCi. This regimen approached Barzelatto's "intermediate dose" effectiveness in inducing euthyroidism (63%) while producing significant hypothyroidism at one year (21%). Our rate of hypothyroidism was also very high after three years (53%).

In 1981, Rosado and Conde reviewed retrospectively the metabolic status of 73 thyrotoxic patients treated with an average 3.47 mCi dose estimated clinically at the San Juan City Hospital.⁸ At one year, 18% of these subjects turned hypothyroid. The cumulative percentage of hypothyroidism reached 3.2% per year and at the end of 12 years 38% of the patients were hypometabolic.

Although the difference in patient numbers between our study and the latter precludes any significant statistical analysis, our preliminary results suggest that our much higher hypothyroid rate is directly related to our higher average dose (7.6 vs. 3.47 mCi).

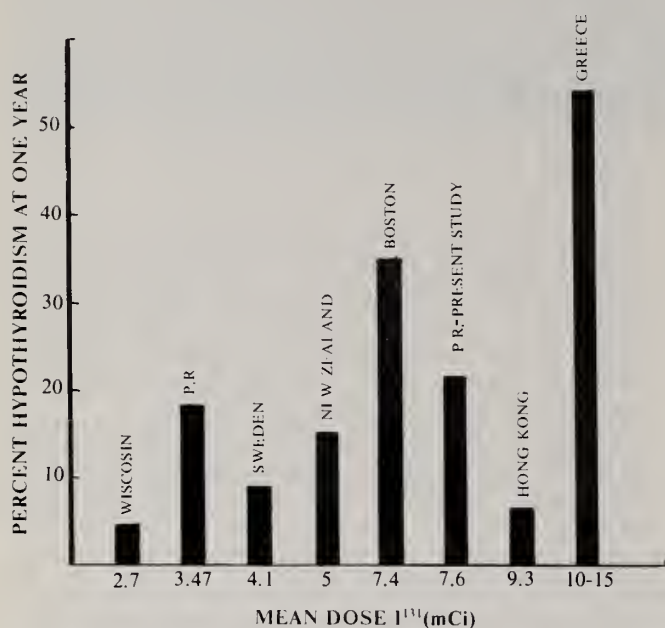
The specific population's sensitivity to a given dose of radioiodine is the other important factor that becomes evident as we review the recent world literature.⁸⁻¹⁷ (Table II). Although generally speaking, we see the greater percentage of hypothyroidism in patients receiving higher I^{131} dosis, certain groups show dissimilar responses. For example, Best et al.⁹ found a post- I^{131} hypothyroidism rate of 6% in Hong Kong Chinese receiving an average dose of 9.3 mCi while, at Boston, Cevallos¹⁰ reported a much higher rate of 33% using a

Table II

Post-Radioactive Iodine Hypothyroidism Rate				
Group	No. of Patients	Dose Given	% Hypothyroidism (1 year)	Dose Calculation Method
Glennon ¹¹ (1972)	55	2.7 mCi	2.7%	Fixed-dose
Best ⁹ (1981)	1396	9.3 mCi	6%	I uptake
Beling ¹² (1961)	791	4.1 mCi	7.46%	Palpation
Smith ¹³ (1967)	276	140 uCi/gram	8%	Palpation
Goolden ¹⁴ (1986)	261	60-300uCi/gram	10%	Palpation
Turner ¹⁵ (1985)	76	5 mCi	14%	Fixed-dose
Rosado ⁸ (1981)	73	3.47 mCi	18%	Palpation
Present series	19	7.6 mCi	21%	Volumetric
Cevallos ¹⁰ (1974)	35	7.4 mCi	33%	Palpation
Ratliff ¹⁶ (1986)	96	15 mCi	48%	Fixed-dose
Alevizaki ¹⁷ (1985)	1168	300 uCi/gram	54.4%	Palpation

lesser 7.4 mCi dose (Figure 2). Ethnic, geographic and nutritional factors are most probably responsible for these differences.

Figure 2



Regional Incidence of Post-I¹³¹ Hypothyroidism at One Year Interval

In our study we did not consider the iodine uptake of our patients in calculating the I¹³¹ dose. Perhaps, including this variable or reducing the 200 uCi/cm³ dose would have resulted in a lower incidence of hypothyroidism. It could have also resulted in a lower cure rate, making us go back to the philosophical question: Shall we cure thyrotoxicosis and ignore the hypothyroidism side effect as an unavoidable and treatable "lesser evil" or shall we continue to search for that "fine line" that divides clinical cure from hypothyroidism?

We hope that future, long-term, controlled studies, using scientific calculation of the variables involved in determining the I¹³¹ dose for the treatment of thyrotoxicosis, will provide the answer to this question.

Resumen: Presentamos nuestra experiencia preliminar con un nuevo método para estimar la dosis de yodo radioactivo (I¹³¹) en el tratamiento de tirotoxicosis utilizando una dosis fija del isótopo por volumen calculado de la glándula tiroidea. Diecinueve pacientes (16 mujeres y 3 hombres) con la enfermedad de Graves fueron incluidos en el protocolo. La dosis calculada de I¹³¹ varió de 2.6 a 14.5 milicurios (mCi) con una dosis promedio de 7.6 mCi. Al final de un año 63% de los pacientes estaban eutiroides y 21% hipotiroideos. Los pacientes fueron evaluados periódicamente hasta un máximo de tres años. Comparamos nuestros resultados con los de otros estudios informados en la literatura mundial.

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Non-Steroidal Anti-Inflammatory Drugs Induced Gastropathy: Endoscopic Findings in Rheumatic Patients

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Abstract: Fifteen to twenty millions tablets of aspirin and 66.5 millions prescriptions of non-steroidal anti-inflammatory (NSAID) drugs are used in the United States each year. These drugs have been associated with acute and chronic gastrointestinal injury making gastrointestinal complaints their most common side effect. In this article we will discuss the possible pathogenesis of this injury, the therapeutic management and our endoscopic observation in rheumatic patients using these medications at San Pablo Medical Center.

Fifteen to twenty billion tablets of aspirin are consumed each year in the United States. Non-salicylate NSAID's (non-steroidal anti-inflammatory drugs) now accounts for more than 4% of the total number of prescriptions written, amounting to 66.5 million prescriptions.¹ NSAID's have been associated with both acute and chronic gastrointestinal mucosal injury, thus GI symptoms becoming the most common adverse effect with this therapy.

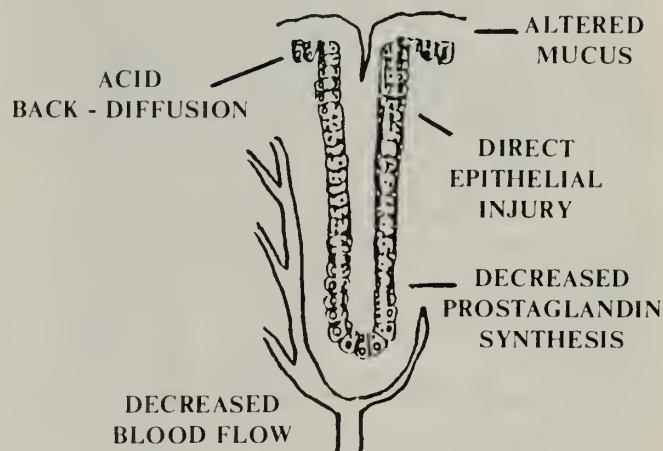
The high prevalence of NSAID induced gastropathy first became apparent in the 1970's when drugs such as phenylbutazone, indomethacin and aspirin were commonly used. Since that time, newer and supposedly safer medications have been introduced, but the types of mucosal damage have not changed. The purpose of this article is to discuss the possible pathogenesis of gastric mucosal injury, its therapeutic management and our endoscopic observations in rheumatic patients using these medications at San Pablo Medical Center.

Pathogenesis

The pathogenesis of NSAID induced gastropathy is a complex multiphasic process that involves a combination of biochemical, functional and structural changes. Aspirin causes mucosal damage breakdown of the gastric mucosal barrier causing back diffusion of hydrogen ions and a drop in the gastric mucosal potential difference.² The data is fragmented regarding mucosal damage by NSAID's. It has been speculated that the damage may be related to inhibition of prostaglandin synthesis.³ Other mechanisms maybe direct epithelial injury, decrease mucosal blood flow, and diminished thickness of the gastric-mucus layer.⁴ (See figure 1)

It is known that NSAID's can cause acute gastric mucosal damage ranging from small sub-mucosal

Figure 1 Mechanism of NSAID Mucosal Injury



hemorrhages having minimal clinical significance to large gastric ulcers.⁵ Whereas minor injury may be repaired via restitution of the surface epithelium, deeper damage may involve vascular structures with subsequent major bleeding. Of far greater concern are the potential risks associated with long term NSAID's therapy as in the treatment of patients with rheumatoid arthritis.

The transition between acute and chronic injury is marked by the process of adaptation during which the amount of damage incurred stabilizes. A common element observed in the pathogenesis of cell injury is inhibition of oxidative phosphorylation, which leads to a decrease in the level of adenosine tri-phosphate (ATP). As a result the cellular potassium concentration decreases, the sodium concentration increases resulting in cellular edema. Subsequent leaks in various membranes results in massive influx of calcium in the cytoplasm. Activation of phospholipases follows with further increases in membrane permeability. Greater influx of calcium and water result in irreversible injury and cell death.⁴

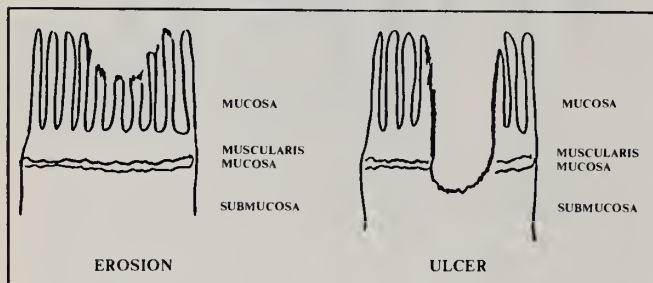
Superficial lesions that affect the surface layers of the mucosa are generally self-limiting; the surface cells easily sloughed off and rapidly replaced.⁶ Injury into the deeper cells results in erosions or should the injury penetrate the muscularis mucosa, ulcers. Involvement of the endothelial cells of the vascular tree lying beneath the surface of the mucosa result in hemorrhage, these vascular disturbances being of greater concern.

Endoscopic Observations

It is known to exist a lack of correlation between gastrointestinal symptoms and endoscopic findings in NSAID induced gastropathy.⁷ Endoscopy may be able to detect several types of lesions. Visible breaks or frank submucosal hemorrhages in the mucosa indicate erosive changes, whereas the absence of breaks with erythema and edema is associated with non-erosive inflammation.⁶

Erosions are defined as shallow mucosal defects that do not extend through the muscularis mucosa while lesions that reach this depth are classified as ulcers (See figure 2). Typically, erosions appear as flat or minimally depressed white spots surrounded by a red halo and they are usually multiple. If hemorrhage has recently occurred, the erosions may appear with a black base. In case of non-erosive gastritis, no breaks are seen, the mucosa itself looks redish and inflamed. Most of the times this process is only evident histologically confirming that the correlation of histology and endoscopy is poor.

Figure 2 The difference between an erosion and an ulcer



This type of non-erosive gastritis appear to have an important influence on the pathogenesis of drug induced gastropathy. So theoretically the effect of an NSAID on the gastric mucosa may be determined in part by the state of the mucosa prior to the administration of the agent.

There is some conflicting and limited data concerning esophageal inflammation in patients taking NSAID's.⁹ It appears that the effect of NSAID's on the esophagus is not the result of topical contact. The time of contact with esophageal mucosal lining under usual circumstances is several seconds, which is certainly not enough time to result in ulceration. It is more likely that the mechanism of injury is an indirect one stemming from the effect of NSAID on the gastric mucosa. The gastric injury may lead to transmural inflammation and impaired motility with endoscopic findings ranging from small esophageal ulcerations to frank strictures.

Report of Endoscopic observations in Rheumatic Patients

Most endoscopic studies of rheumatic patients on regular NSAID therapy have reported a degree of gastric injury ranging from 30-50%. The first two studies published on this subject were reported by Silvoso with a 40% incidence of erosions and a 17% of ulcers.¹⁰ Another by Caruso with a 41% incidence of either ulcers or erosions.¹¹ In both studies all patients were taking at least one of twelve NSAID's or combination. A lack of correlation between endoscopic findings and clinical symptoms

was corroborated. A recent report by Smith in 65 rheumatic patients followed this same pattern of previous studies despite earlier endoscopic approach in patients with symptoms. Our experience at San Pablo Medical Center has included 60 consecutive patients referred from a rheumatology clinic all of them using NSAID's for more than 2 weeks, in which persistent gastric distress or the development of symptoms indicative of ulcer disease after NSAID's was started. Patients who tested positive for occult blood or had a significant drop in Hemoglobin levels while on NSAID's were included. All patients underwent esophagogastroduodenoscopy and the endoscopic findings were reported according to Weinstein's classification.⁸ (See Table I) The incidence of erosions was estimated at 27% and of ulcers at 13% comparable to previous reports.

Table I

Endoscopic findings in Rheumatic Patients at San Pablo Medical Center				
#of Pts.	Normal	Non-Erosive Gastritis	Erosions	Ulcers
60	10 (17%)	26 (43%)	16 (27%)	8 (13%)

Management

Pharmacologic therapy has been the mainstay used to treat NSAID induced gastropathy. Antacids neutralize gastric acid and reduce pepsin activity. In addition they increase gastric secretion, bind bile salts and provide mucosal protection.¹³ They also tend to interact with a number of other agents, like when administered with salicylates they increase renal clearance administered with salicylates they increase renal clearance resulting in reduced serum levels. The aluminum and magnesium hydrochloride compounds contained in some antacids reduce the bioavailability of indomethacin. The H2 receptor blockers, cimetidine and ranitidine act by blocking the histamine receptor sites at the parietal gastric cell. The resulting effect include a reduction in acid production, pepsin and intrinsic factor with a resultant increase in gastric pH. H2 blockers have been shown to affect the gastric damage induced by NSAID's. The protective effect maybe mediated by its antisecretory effect or other aspects of mucosal cytoprotection.

The cytoprotective drug sucralfate is a complex salt with adhesive properties that forms a protective barrier at the ulcer site, preventing back diffusion of hydrogen ions, inhibiting the action of pepsin, absorbing bile salts and stimulating prostaglandin synthesis.¹⁴ Several strategies can be tried before initiating adjunctive therapy in patients with NSAID induced gastropathy. First patients should be advised to take NSAID with their meals and adequate fluids. They should be urged to maintain an upright position when taking the medication to avoid excessive drug exposure in the esophagus as seen in elderly patients taking medications while supine in bed. Avoidance of alcoholic beverages and restriction of smoking is

mandatory. Prescribing smaller and, more frequent doses should also ameliorate symptoms and consequences. Periodic hemoglobin monitoring and stool testing for occult blood are important measures in patients taking NSAID chronically to avoid potential life threatening hemorrhage.

Conclusions

NSAID induced gastropathy is a well defined clinical entity. The pathogenesis appears to be related to a variety of factors including breakdown of gastric mucosal barrier, back diffusion of hydrogen ions, inhibitions of prostaglandin synthesis, direct injury and decreased blood flow. The endoscopic lesions in patients receiving NSAID's are fairly definable, ranging from erythema, erosions or frank ulcers. There is however, a tremendous discrepancy between the numbers of visible lesions and the histologic findings, as well between the number and types of visible lesions and the patient's symptomatology. Therapy should be directed to pharmacologic measures which tend to improve cytoprotection and reduce secretory capacity and non-pharmacologic measures to counteract NSAID's gastric injury.

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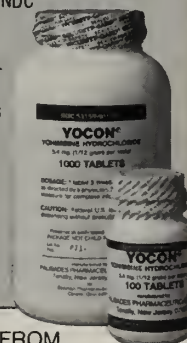
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

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Bone Marrow Involvement in Small Cell Carcinoma of Lung

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César O. Freytes, MD**
Ronald H. Lands, MD***

Small cell carcinoma of the lung (SCLC) is a distinct clinico-pathologic entity which accounts for 20-25% of lung cancer. Some of the features which characterize this disease include its apparent neuro-endocrine differentiation, its responsiveness to anti-neoplastic therapy and propensity for systemic metastasis.¹ The most important prognostic factor in these patients is the extent of tumor dissemination at the time of diagnosis. The median survival of patients with disease beyond the ipsilateral chest is 24-40 weeks with survival of less than 1% beyond 24 months.²

Bone marrow examination is frequently included in the pretherapy staging of small cell carcinoma of the lung. The reported frequency of involvement ranges between 13-26%. Several studies have suggested that only a minority of patients with small cell carcinoma have extensive disease based on marrow examination alone. Campling et al reported only 7 out of 403 patients (1.7%) whose disease stage was upgraded based on marrow examination.³

Similar results were published by Idhe et al with only 1 out of 73 patients where the bone marrow exam upgraded the disease stage.⁴ Furthermore the median survival of patients with marrow involvement is quite similar to those patients with extensive disease without marrow involvement. Thus the role of bone marrow examination in staging patients with small cell carcinoma of the lung has questioned.

As part of several ongoing institutional clinical trials we have examined the impact bone marrow examination has had in consecutive patients with small cell carcinoma of the lungs. Emphasis on frequency, clinical correlation and comparative survival among the patients has been given.

Materials and Methods

From December 1984 to December 1986, a diagnosis of small cell carcinoma of the lung was histologically or cytologically confirmed in eighty consecutive patients. Seventy-nine of these patients underwent pretherapy staging with a complete history, physical examination, chest roentgenogram, brain computerized tomography, liver-spleen scan or abdominal CT Scans, bone scan, bilateral bone marrow aspirates and biopsies, serum

chemistries, liver functions test and complete blood count. The remaining patient did not have a bone marrow exam as part of his pretherapy evaluation so he was excluded.

All seventy-nine patients received therapy according to one of the 3 ongoing institutional clinical trials. Informed consent was obtained from all patients prior to study entry. Details of each of these clinical trials will be subject of a separate report. Due to the similarity in the overall survival among these trials a correlation between bone marrow findings and survival is included in this report. Survival duration was measured from the date of first chemotherapy.

Hemogram and serum chemistries were done by standards methods in the hospital laboratory. Statistical analysis was done by the Wilcoxon non Paired Rank Sum Test.

Results

Detection of Bone Marrow Metastasis

Forty-eight percent of patients were judged to have extensive disease at the time of diagnosis (38/79). Of these 38 patients, 19 were found to have tumor in the marrow by aspirate, biopsy or both (19/38) or 50%. It is of interest that 5 of these 38 patients with extensive disease had bone marrow involvement as their only site of extra-thoracic disease (13%) (Table I). Thus 6.3% of the entire 79 patients study population were upgraded in disease stage based on bone marrow examination. This represents 13% of patients with extensive disease.

In Table 2 a comparison of the marrow aspirate and marrow biopsy among patients with proven bone marrow involvement by SCLC is made. There is a false negative rate of 32% for the aspirate examination as compared to 5% for the biopsy. It is of interest to note that 6 of these 19 patients (32%) marrow involvement was detected in only one side. As mentioned in the methodology all of our patients underwent bilateral examination.

Table I

Bone Marrow Involvement by SCLC			
	Patients	Marrow Involvement Patients (%)	Marrow Only
Limited	41	—	—
Extensive	38	19 (50%)	5 (13%)
Total	79	19	5

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Table 2

Comparison of Marrow Aspirate and Marrow Biopsy in Patients with Known Bone Marrow Involvement

	Aspirate PTS (%)	Biopsy PTS (%)
Positive	13 (68%)	18 (95%)
Negative	6 (32%)	1 (5%)
Total	19	19

Correlation with Hematologic Findings

The hemoglobin, total WBC and platelet counts were examined among our patients and correlations were made to the presence or absence of marrow involvement (Table 3). The average hemoglobin in patients with extensive disease and involvement bone marrow was 12.5gm% (range 10-16.5), average platelet count 350,000/mm³ (42,000-580,000) and mean WBC 9,157/mm³ (3,600-23,400). In patients with extensive disease without marrow involvement the mean hemoglobin 14.1 gm% (10.5-18.9), mean platelet count 306,000/mm³ (160,000-528,000) and mean WBC 8,363 mm³ (3,700-17,300). The lower hemoglobin in the patients with marrow involvement was the only significant difference (p=.03) in this group of patients. For comparison the hemogram values of patients with limited disease and bone marrow as only site of extrathoracic disease is included.

Table 3

Comparison of Hematologic Variables in Patients with and Without Marrow Involvement by SCLC

Stage	Means		
	WBC (mm ³)	Platelets (mm ³)	Hemoglobin (gm %)
Extensive			
Marrow (+)	9,157	350,000	12.5
	*N.S.	*N.S.	**p = .03
Marrow (-)	8,363	306,000	14.1
Marrow Only	7,360	337,200	12.8
Limited	7,900	345,615	13.9

*N.S. - Non Significant

**By the Wilcoxon Non Paired Rank Sum Test

Correlation with LDH and GGTP

In patients with extensive disease there was a significantly higher level of LDH in patients with marrow involvement (671 vs 140 p=.006). No significant difference was detected for other chemistries. The results of GGTP are included in table 4. When patients were analysed as having a normal or abnormal level of these enzymes no specific and reliable chemistry would predict the presence of marrow involvement. A substantial majority of patients with marrow involvement had some elevation of LDH or GGTP. A large number of patients without marrow disease, or limited disease had elevation of these enzymes.

Table 4

Comparison of LDH and GGTP in Patients with and Without Marrow Involvement by SCLC

Stage	LDH (U/L)	GGTP (U/L)	Abnormal LDH (#PTS)	Abnormal GGTP (#PTS)
Extensive				
Marrow (+)	671	229	14/19 (74%)	14/17 (80%)
	**P=.006	*N.S.		
Marrow (-)	140	103	9/18 (50%)	7/16 (44%)
Marrow Only	259	52	2/5 (40%)	3/5 (60%)
Limited	—	—	12/34 (34%)	9/36 (25%)

*N.S. - Non Significant

**By the Wilcoxon Non Paired Rank Sum Test

Correlation with Organ Involvement

In the group of 38 patients with extensive disease 5 (13%) had the marrow as the only site of extrathoracic disease. When taken as part of the whole group of 79 patients, this represent 5% of patients. Table 5

Of the 19 patients with extensive disease involving the marrow 12 had liver metastasis (63%), 3 had CNS metastasis (16%) and 10 (53%) had metastasis to bone. Of the remaining 19 patients with extensive disease not involving the marrow 7 had liver metastasis (37%), 11 had CNS metastasis (61%) and 8 had bone metastasis (44%). As presented in the methodology section the presence of bone metastasis was defined by the nature of the staging bone scan.

Table 5

Correlation with Organ Involvement Among Patients with Extensive Disease

Stage	Organ		
Extensive	Liver	Brain	Bone
Marrow (+)	12/19 (63%)	3/19 (16%)	10/19 (53%)
	N.S.		N.S.
Marrow (-)	7/19 (37%)	11/19 (61%)	3/19 (44%)
Marrow Only	0/5	0/5	0/5

Correlation with Response and Median Survival

We have analyzed our data according to the number of patients achieving a complete remission from the disease as well as the median survival (Table VI). In patients with extensive disease a complete response was seen in 18% with a corresponding median survival of 19 weeks. In patients with limited disease a CR of 55% was seen with a 52 week median survival. It's of interest that among the group of patients with the marrow as only site of disease the CR and median survival of 40% and 40 weeks appears intermediate among the former two groups.

Table 6

Correlation in SCLC Patients with Complete Response and Survival

Stage	Complete Response (%)	Median Survival (Weeks)
Extensive	18%	19 Weeks
Marrow (+)	26%	20 Weeks
Marrow (-)	11%	16 Weeks
Marrow Only	40%	40 Weeks
Limited	55%	52 Weeks

Discussion

The prognostic implications of detecting small cell carcinoma beyond the primary and adjacent lymphatic drainage site are well documented.^{1, 2} Whether or not a bone marrow diagnostic procedure is indicated in the workup of patients with small cell carcinoma of the lung has been debated extensively for the past 10 years.^{5, 6, 7} During the past two years we have been able to examine some of these issues, in 79 consecutive patients with small cell carcinoma. All of these patients have had bilateral exams because of protocol requirements. During this period, 19 patients were found to have bone marrow involvement with small cell carcinoma. The overall incidence of bone marrow disease of 24% and the incidence of 50% in extensive stage is comparable to other studies in which bilateral exams were done as a matter of routine.

In this series 5/79 (6%) patients were positive in the bone marrow as their only site extrathoracic disease. Stated another way 5/38 (13%) of our extensive disease patients were extensive by virtue of their marrow positivity. This data suggest that bone marrow examination should remain part of the standard pretherapy staging procedures in these patients. All of our patients underwent bilateral marrow examination as part of protocol requirements. Of the 19 patients with marrow disease, 6 patients had tumor diagnosed on only one side, implying that a unilateral biopsy in the negative side would have been interpreted incorrectly, as meaning that the marrow was not involved. Only two of these 6 patients, however would have been incorrectly staged as having limited as compared to extensive disease. Thus bilateral marrow exams in our patient population upgraded only 2 of 79 (2.5%) patients from limited to extensive disease. The need for bilateral marrow examination remains a matter of speculation. There are many studies citing LDH elevations as a marker of bone marrow metastasis.⁸ There are others that cite its negativity as being more specific for indicating limited disease.¹ Our series showed an abnormal LDH in 14/17 (74%) patients with known bone marrow involvement compared to 44% of those patients with extensive disease without bone marrow involvement and 25% of patients with limited disease. This data suggest that LDH is not a

reliable predictor of bone marrow involvement in this disease. Our data does confirm that patients with bone marrow disease will have a statistically significant higher serum level of LDH.⁸

We attempted to discriminate between marrows with tumor and those without by looking at the WBC, platelet count and hemoglobin. Our studies did not confirm this, but there was a significant reduction in hemoglobin concentration in patients with bone marrow metastasis.

By comparison we examined the GGTP as a predictor of bone marrow metastasis. 73.6% of the patients with extensive disease and positive bone marrows had a clearly abnormal GGTP while 50% of the extensive stage patients with negative bone marrow had elevated enzyme, 34% of all the limited patients had an abnormal GGTP. These differences were not significant enough to allow one to discriminate subsets with or without bone marrow involvement.

The association of bone marrow positivity and patterns of metastasis has been studied. Our study did not statistically confirm previous evidence that tumor in the bone marrow is more frequently associated with liver involvement (63%) than when the bone marrow is negative (37%). Bone metastasis occurred independently in patients with or without marrow metastasis. Brain metastasis occurred in 61% of the extensive patients who did not have marrow involvement while it occurred in only 16% of those who had tumor in the bone marrow at diagnosis. While this observation proved to be highly significant it may be an aberration since an inordinate number of our patients presented with CNS metastasis at the time of diagnosis.

The definition of extensive or limited disease provides prognostic information. We attempted to determine whether the presence of tumor in the marrow provided additional prognostic information in the extensive group of patients. The overall median survival observed in our series of limited stage patients was 52 weeks. The overall survival for our extensive stage patients was 19 weeks.

Among patients with extensive disease the presence or absence of bone marrow metastasis did not influence long term survival or complete response when examined as subgroups of the extensive patients. Long term survival comparisons between these subgroups of patients with extensive disease revealed a median survival of 20 weeks for patients with positive bone marrow and a median survival of 16 weeks for people with metastasis to sites other than the marrow. While these differences were not significant, there was a subset of five patients with bone marrow as only site of metastasis. Although the number is small, their overall survival appears to be better than the other group of patients with extensive disease. In conclusion, this study reconfirms that an abnormal LDH, in spite of it being non-specific is associated with bone marrow metastasis. The study demonstrates a reduction in the hemoglobin concentration as being an indicator of tumor in the marrow cavity. A subgroup of patients with extensive disease and bone marrow as the only site of metastatic disease is present, whose response to therapy and median survival appears intermediate between patients with otherwise extensive disease and limited disease.

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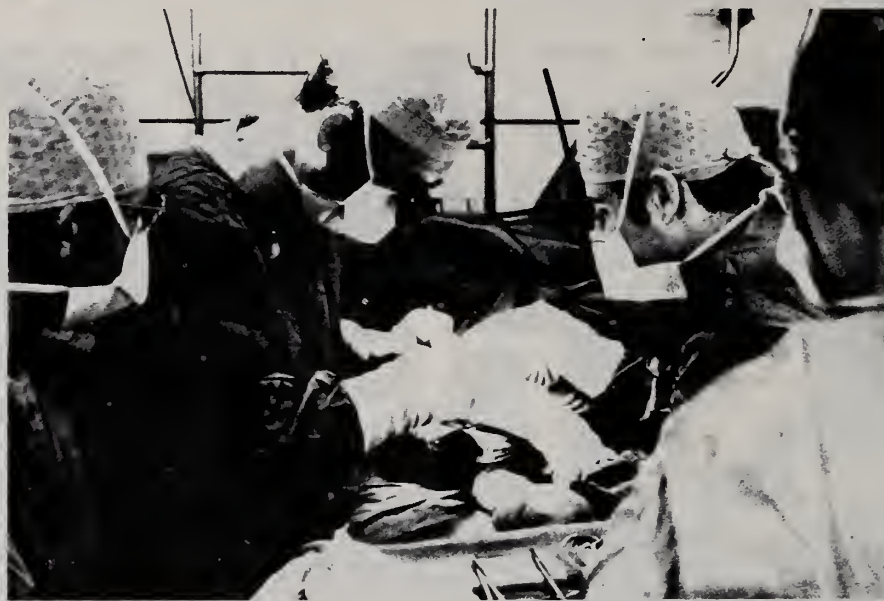


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An Intervention to Increase Mammography Screening in a Family Medicine Residency Program

Miguel V. Buxeda, MD

Abstract: Record audit, peer comparison feedback and system changes were used to increase the effectiveness of an educational intervention aimed at increasing the compliance of Family Practice Residents with American Cancer Society mammography screening guidelines.

Previous to the intervention, the residents adequately screened 23% of the women over age thirty five which they encountered during regularly scheduled appointments. After the intervention, 59% of the women were adequately screened. All the residents improved their performance and improvement occurred in all age groups audited. The improvements were statistically significant. ($P < .001$)

In 1988 an estimated 135,000 new cases of invasive breast cancer will be diagnosed in American women. There will be an estimated 42,000 deaths from this disease. Breast cancer is the most common female malignancy. It is the second leading cause of cancer deaths in women.¹

Surgery, chemotherapy and radiotherapy have not been successful in decreasing general mortality. Age adjusted breast cancer death rates have remained constant during the past four decades. To date, there are no proven technologies to reduce the incidence of this disease.

Early detection has been shown to decrease mortality and increase survival in women with breast cancer. Routine breast self examinations and periodical physician examination have long been advocated as useful methods of preventive medicine.

Mammography offers the added benefit of being able to detect lesions at an earlier stage of development. The medical community however has been very slow in implementing the utilization of this valuable screening tool. A nation wide survey of primary care physicians showed that only 11% said they observed American Cancer Society guidelines for mammography screening.² Even in the highest risk age group, that of women over 50 years of age, it is estimated that only 15-20% have ever had a mammography.³

Resistance to implementation of mammography screening has been explained in terms of issues of excessive radiation, lack of effectiveness, poor patient compliance and cost. But it has been shown to be a safe, effective and well accepted for of preventive medicine.⁴⁻¹² Cost benefit analysis have been done which show that the

costs for screening a large population of asymptomatic women are well within the cost-benefit range accepted for other areas within the medical care system.¹³

The main reason why American women are not receiving the benefit of this test is that physicians are not ordering it. A recent survey of women has pointed out that the absence of physician recommendations is the greatest deterrent to the current use of mammography.¹⁴

Scientifically tested methodologies of medical education have to be implemented in order to increase physician compliance. Educational interventions need to accomplish not only intellectual enlightenment but also effective changes in physicians' patterns of practice.

Various studies and review articles have questioned the value of educational interventions in improving physicians clinical behavior.¹⁵⁻¹⁹ But alternations in the organization and implementation of these interventions can significantly increase their effectiveness.

Effective educational efforts have in common the previous identification of specific deficiencies in physician practices, the specification of clear goals and objectives, the use of relevant learning methods and the existence of a systematic effort to evaluate learner achievement.²⁰⁻²¹

Record audits have consistently been shown to be useful in identifying physicians deficiencies and aiding the process of medical education.²⁰⁻³⁰ Because physicians overestimate the degree to which they order screening tests, they fail to take needed corrective actions.

Peer comparison feedback has likewise been shown to be effective in improving physicians performance.²⁴ When individual doctors compare their actual performance with those of their peers, more effort is made to bring future performance to acceptable standards.

System changes have also been advocated to increase physician compliance with preventive medicine guidelines.²⁵ Using this approach, changes in the physicians' environment or routine office practice can serve as behavioral cues that will systematically reinforce the need to order screening tests.

Purpose of the Study

The purpose of the study was to determine whether an educational intervention which incorporated record audit, peer comparison feedback and system changes could improve mammography screening of asymptomatic women in a Family Medicine Residency Program.

Material and Methods

The subjects of this study were seven second and third year residents in the San Pablo Hospital Family Medicine Residency Program in Bayamón, Puerto Rico. The tota-

lity of ten second and third year residents could not be included because two third year residents finished their training in the middle of the study and another resident was on vacation at the time of the educational intervention.

During six weeks, from October 1 to November 12, 1987 all records of women aged thirty five or older seen with appointments by the subjects at the Family Practice Center were audited. Women seen by residents on a walk-in or emergency room basis were not audited because our usual practice is to schedule these patients for routine health maintenance during scheduled appointments. Credit was given to the resident if a mammography was ordered on the date of the audit, or if the record showed that it has been ordered in previous visits by the resident in such a way as to comply with American Cancer Society guidelines at the time of the audit. An individual record was kept of each physician's performance in following the guidelines for screening mammography established by the American Cancer Society. Separate figures were kept of the three age groups for which different guidelines are recommended: women aged 35-39, women aged 40-49 and women aged 50 or older.

An educational intervention was implemented on January 22, 1988. It consisted of seven parts:

1. A pretest was given to the residents. It was designed to determine the residents knowledge of American Cancer Society guidelines for preventive mammography, inquire about any discrepancies they may have with them, and establish their perceptions of how well they had complied with these standards.
2. After the pretest, each physician was presented with the results of his or her individual performance audit along with a set of graphs that would enable them to compare their performance with those of their peers.
3. The group participated in a brief discussion of the audit findings.
4. Two medical education conferences were presented. The first one summarized the epidemiological and research data which supports the use of mammography as an effective preventive medicine tool. The second consisted of an audiovisual program prepared by the American College of Radiology on "Clinical Mammography" and which was given by our Hospital's Radiology staff.
5. A discussion of the main issues and deterrents to the screening of asymptomatic women followed, during which we also had the participation of a patient representative, a woman with bilateral mastectomy whose daughter had also had a mastectomy to remove breast cancer.
6. A post test was given to the residents. This was identical to the pretest and was designed to show any changes in knowledge or attitudes of the participants.
7. Review articles concerning the topic of mammography screening of asymptomatic women were distributed.

Following the intervention, two system changes were made in our Family Practice Center. One was the placement of a poster in the patients' waiting room which

urged women to have a mammography performed. This poster was clearly visible to physicians on their way in and out of the clinic. The other change consisted of the provision of patients education leaflets concerning mammography screening. These leaflets were placed on top of all physicians desks along with the usual prescription and laboratory forms. Physicians were urged to distribute these forms to patients as part of their routine medical care.

A second record audit was performed on the six weeks from January 25, 1988 to March 4, 1988.

For each of the time periods during which the records were audited, the datum for each resident was a proportion the total number of mammographies ordered in asymptomatic women aged thirty fives or older to the total number of women.

A proportion was also calculated of the women adequately screened in each of the three age groups for which different guidelines have been established by the American Cancer Society: women aged 35-39, women aged 40-49, and women aged 50 or over.

The results of the Pretest and Post test were compiled in order to determine deficiencies in physicians' knowledge of attitudes and changes in these after the educational interventions.

Paired tests were performed to compare residents' performances before and after the intervention for the totality of women seen and also for each of the three age groups audited.

Results

The pretest showed that all residents could adequately identify American Cancer Society guidelines for screening asymptomatic women with mammographies, and that they all agreed on the adequacy of these guidelines. Their average estimate of them women they adequately screened was 58%.

The post test showed that all residents realized their actual performance during the time period audited.

The results of the intervention are shown in figures 1 and 2. Previous to the intervention 36 of 156 or 23% of women were adequately screened. After the intervention 82 of 140 or 59% of women were ordered preventive mammographies.

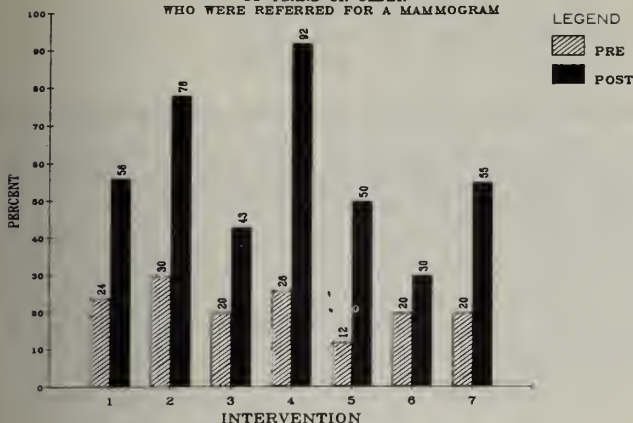
The improvement occurred in all age groups audited. After the intervention, 67% of women aged 35-39 were adequately screened, 54% of women aged 40-49, and 59% of women aged 50 or over.

All the residents improved their performances. The mean improvement in performance was 148% with the highest improvement at 254%, the lowest at 50%, and the median at 150%.

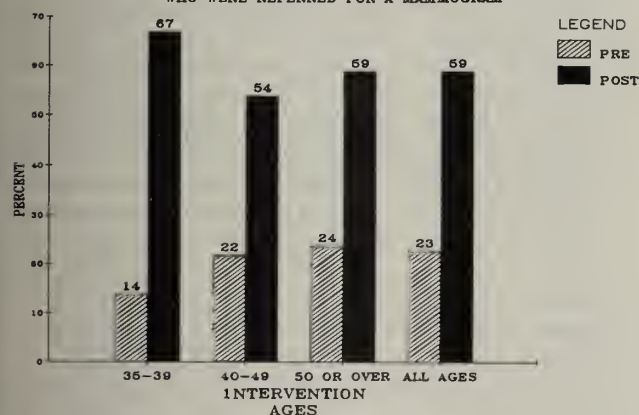
The paired tests showed that significant differences were present between the preintervention and postinterventions mean scores. ($p < .001$).

The improvement among the different age groups was also significant ($p < .05$).

PERCENTAGE OF ASYMPTOMATIC FEMALE PATIENTS
SEEN ON SCHEDULED APPOINTMENTS
35 YEARS OR OLDER
WHO WERE REFERRED FOR A MAMMOGRAM



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Discussion

The preintervention screening behavior of the residents audited in this study was not caused by lack of knowledge or disagreement with American Cancer Society guidelines for ordering preventive mammographies. Rather, this study shows that it was caused by complacency on their part and an overestimation of their actual practice pattern. These findings are consistent with other research which also has found that physicians overestimate the quality of their practices.²⁶

When confronted with the results of their individual and peer audits and when presented with an educational intervention which emphasized the need for the routine utilization of this procedure, they responded with a significant improvement in their performances.

A previous study also used a one session intervention to improve the mammography screening of Family Practice residents.²⁷ Fox, Tsou and Klos emphasized the development of group consensus in their educational intervention and followed it up with two behavioral cues

consisting of (1) asking physicians to keep a patient log for one week and (2) sending physicians a memorandum two weeks after the educational session. Following this intervention, these researchers were able to increase mammography screening from 3.6% to 10.8% of the totality of women seen.

The results of the two studies are not directly comparable because the previous one included all women seen by residents, including nonscheduled encounters.

The methodology of the educational intervention also differed. The previous study did not utilize record audit and peer comparison feedback. The environmental cues designed to reinforce learned behavior were different. Both studies show that educational interventions can increase compliance with established guidelines for mammography screening.

The results of this study are consistent with those found by Pointon and Ogle.²⁵ In their study, they audited compliance with Center for Disease Control standards for Chlamydia testing on obstetrical patients. They found that compliance increased dramatically after individual feedback and also after a system change in the office practice.

Geertsman et al have studied how physicians change their practice behavior.²⁸ They conclude that the first fundamental step in changing behavior is the provision of feedback in such a way that physicians feel dissatisfaction with some aspect of their practice. They call this part of the changes process priming.

Individual record audit and peer comparison feedback are powerful priming tools. Their use should be encouraged in improving physicians performance and increasing the effectiveness of medical education.

It cannot be delineated how much of the improvement in this study was due to the cues designed to reinforce the ordering of mammographies. The cues became a part of the physicians immediate environment. The simplicity of such an intervention and the added benefit of patient education certainly advocates their use.

The study has multiple limitations, some of which I will address. First of all was the small number of the sample size. This could not be avoided because of time limitations and the fact that the sample included all the women seen by the residents during the time of the study.

The second limitation is the fact that the improved performance was observed during the six weeks which followed the educational intervention. Follow up audits need to be done in order to demonstrate how permanent are the changes in the residents behavior.

The third limitation of this study was that no control group was utilized. This was not possible because of the small number of residents in our Residency, the fact that educational interventions are given routinely to the group as a whole, and the impossibility of isolating a control group from the behavioral cues utilized. No extraneous influences could be ascertained that would explain or influence the residents change in behavior. There were no educational efforts by other groups that could influence their screening practice, and the widely publicized case of breast cancer of the President's wife Nancy Reagan occurred previous to the baseline audit performed in this study.

Conclusion

Record audit, peer comparison feedback and system changes improve the quality and effectiveness of educational interventions aimed at increasing compliance with established mammography screening guidelines.

The use of these methodologies enhances the acquisition of necessary preventive medicine skills by resident physicians. They could also be used to improve other areas of care where residents' performances are found to be substandard.

It remains to be determined whether these techniques can bring about changes in the pattern of practice of physicians who have finished their residency training.

It is impossible to audit private solo physicians unless they voluntarily group themselves for the purposes of improving the quality of their practices. More practical will be the application of these methodologies to group practices or health maintenance organizations.

Resumen: Un grupo de residentes de Medicina de Familia fue sometido a una intervención educativa con el propósito de mejorar su utilización de la mamografía como prueba diagnóstica preventiva. Para fortalecer el impacto de la sesión educativa se utilizó preauditoría de records médicos, comparación con pares y cambios en el medio ambiente.

Antes de la intervención, los residentes ordenaron adecuadamente la mamografía preventiva en el 23% de las mujeres mayores de 35 años que vieron en sus citas médicas. Después de la intervención, se hizo el cernimiento adecuado en el 59% de las mujeres vistas.

Todos los residentes mejoraron su comportamiento y hubo mejoría en todos los grupos de edades de las mujeres. Estas mejorías fueron significativas estadísticamente (P .001).

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REVIEW ARTICLES

Exercise, Sports and Pulmonary Ailments in Children

Pedro M. Mayol, MD
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Abstract: We describe an increased interest in exercise and sports related activities in Puerto Rico in general and specifically within the University of Puerto Rico Medical Sciences Campus and the Pediatric Pulmonary Program. The mechanisms whereby the child's lungs cope with exercise and disease are discussed. Further details for patients with bronchial asthma, cystic fibrosis and tuberculosis are provided. Emphasis is placed upon the ability of the child with pulmonary disease to cope with exercise and the desirability of making appropriate assessments and recommendations that will lead to greater and successful involvement of all children, sick and well, in exercise programs and sports activities.

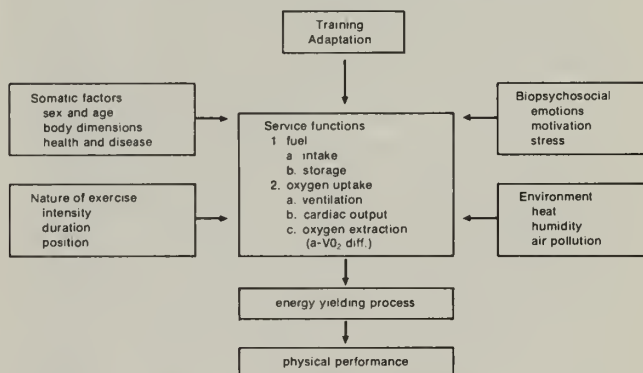
In Puerto Rico, sports activities are an important part of our culture. People of all age groups participate actively in many sports related events. This considerable interest in all kinds of sports has been enhanced recently by the possibility of hosting the XXVII Summer Olympic Games in the year 2004. An enhanced interest coupled with concerns about the health and fitness of our athletes and citizens in the community has led to an increased involvement of the University of Puerto Rico (UPR) Medical Sciences Campus (MSC) in exercise and sports related activities. Since the establishment of the Center for Sports Health and Exercise Sciences, at the Albergue Olímpico in Salinas, (a combined project between the Puerto Rico Olympic Committee and UPR-MSC) the authors have become involved in the intellectually stimulating and professionally challenging endeavor of addressing the needs of our children, the athletes and citizens of the future, in dealing with exercise and pulmonary diseases. We have become more conscious of the fact that the pleasure of exercising and participating in sports is not the exclusive right of the gifted or talented, but the right of all human beings. The purpose

of this communication is to describe the mechanisms whereby the lungs of the child cope with exercise in health and disease.

Factors Related to Exercise and Sports Performance

Participation and performance in sports, regardless of the age of the person or the type of sport, is influenced and determined by different factors (Figure 1).

Figure 1. Factors Related to Exercise



Of particular interest to us are the health-related factors. Respiratory ailments are frequently diagnosed in athletes. Among the most common are upper respiratory infections which as a rule cause only temporary disability. Other pulmonary conditions that affect participation in sports include bronchial asthma, cystic fibrosis, tuberculosis and others less frequently encountered in children. In spite of the above, we wish to stress the fact that the child who suffers from pulmonary disease can participate in sports at different levels ranging from recreational walking to elite performance in competitive sports. A recent example is the U.S. team of the 1984 Summer Olympic Games¹ which included 67 (out of 596) competing athletes with exercise induced asthma (EIA). Forty one of the 67 athletes with EIA won medals (15 gold, 21 silver, and 5 bronze). Gold medals were won by athletes with EIA in basketball, cycling, rowing, swimming, track and field, and wrestling. All athletes

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Supported in part by US Dept HHS, Grant No. MCJ-00950-13-0, "PHS, HRS, BHCDA, MCH" and the Laura M. González Foundation.

received approved medications prior to the events. In a situation like the Olympic Games, where fractions of seconds and centimeters may determine the success of athletes, the control of EIA can be an important factor.

For many parents and the general public, exercise and participation in sports is equated with physical distress. Quite often the parents of the children with pulmonary disease become overprotective, preventing the child from participating in sports. Such limitation of participation reinforces a poor self-image and an unfavorable psychological makeup.

The Lung At Rest and During Exercise

The process of pulmonary ventilation and gas exchange comprises the transport of oxygen into the lung from the external environment and the exchange for carbon dioxide at the alveolar-capillary membrane level.

It is important to ask ourselves, is the lung built reasonably for this function? In the 1983 J Burns Amberson Lecture, Weibel³ addressed this question and came to the following conclusions: a) the walls between alveoli are densely populated with blood; b) the tissue barrier separating air and blood is thin enough; c) the surface of contact is very large; d) the airway and blood vessels allow efficient ventilation and perfusion of gas exchange units. In answering the question, he considered the lung as that part of the respiratory system which takes oxygen from the outside air to the mitochondria in the cells, using the pulmonary circulation as an intermediary step (Figure 2). The lung should maintain a diffusing capacity in proportion to the needs for oxygen transfer from air to blood in order to satisfy the body's oxygen demands. Weibel also hypothesized that an increase in body and lung size has an effect on the alveolar capillary oxygen gradient that is inversely related to the driving force favoring diffusion of oxygen from air to blood. In other words the larger the lung, the lower the diffusing force. This requires a large conductance to fulfill the needs for oxygen uptake in the tissues. It turns out that humans need to maintain a relatively large oxygen diffusing capacity because they cannot achieve as high a driving force as smaller animals. He considered that the lung is not only reasonably, but superbly designed.

During exercise, the increased utilization of oxygen by the tissue (especially the skeletal muscle) and increased production of carbon dioxide impose a demand upon the pulmonary system. This demand is met by increases in the minute ventilation, tidal volume, respiratory rate, pulmonary blood flow and gas exchange.²

Recently, Dempsey⁴ addressed Weibel's original question in a different way. Is the lung built for exercise? Dempsey stated that the pulmonary system is ideally designed and regulated to meet the homeostatic demands during exercise in a normal healthy young adult. To a greater extent, exercise capacity in health is limited by the "weaker links" in the oxygen transport and utilization chain such as cardiac output, peripheral circulation, vascularity and oxidative capacity of the skeletal muscle. Dempsey suggested, that this hierarchy of limiting factors changes as one progresses up in the fitness conti-

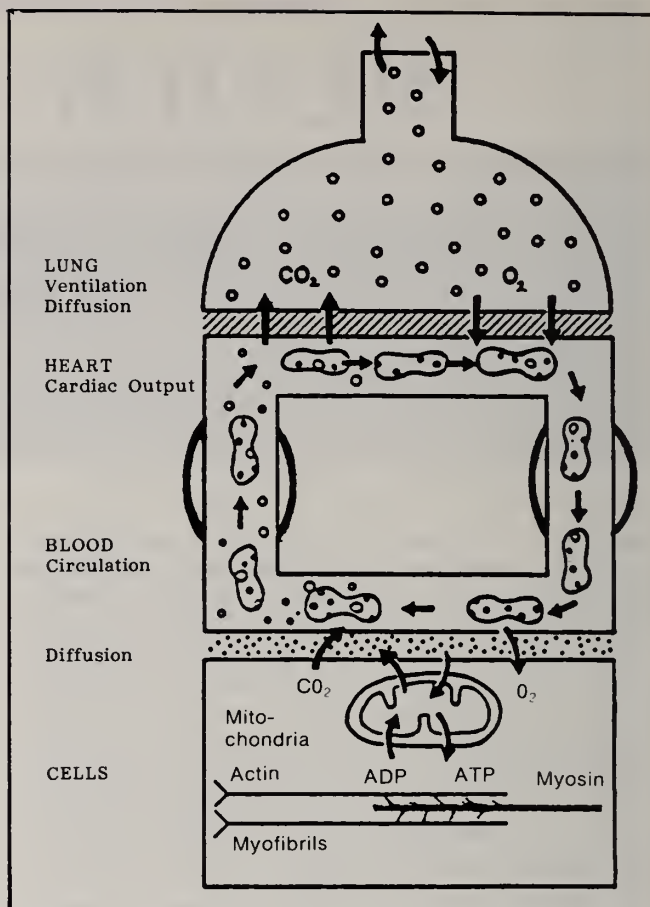


Figure 2. A schematic representation of the stages of oxygen delivery and uptake.

num. This means that the gas exchange capability of the lung, the maximum responsiveness of the chest wall and the ventilatory control system assume a more critical, rate limiting, role in determining maximum oxygen consumption and performance in the well trained athlete.

Several physiological functions have been considered limiting factors during exercise in patients with diseases involving the respiratory system. These functions include pulmonary gas exchange, respiratory mechanics, energetics of respiratory muscles, development of respiratory muscle fatigue, pulmonary circulation and respiratory regulation and sensation.^{5, 6}

In order to evaluate all the possible factors limiting exercise performance in health and disease, sophisticated laboratory equipment is available. However, the importance of a thorough clinical history, physical exam and direct observation and questioning during exercise in the laboratory cannot be overemphasized.

Physiologic Response to Exercise in Children

In order to understand the response of the sick child to exercise, the normal physiologic response must be reviewed, although, due to ethical and methodological constraints, our understanding of children's physiologic response to exercise is still deficient. An excellent review of this matter has been recently published.⁷

The pulmonary response to exercise is quite similar in children and adults. The maximal minute ventilation, when expressed per kilogram of body mass, is about the same in children, adolescents, and adults, but it tends to be higher in children during submaximal exercise.⁸ This suggests a lower ventilatory reserve at a young age. Also noted in children is a relatively greater tachypnea and shallow breathing during submaximal and maximal exercise as reflected by a lower tidal volumen/vital capacity ratio. Moreover, the ventilatory equivalent, a numerical expression of ventilatory efficiency, is higher in children reflecting an inefficient ventilation.

Oxygen uptake is the product of cardiac output and arteriovenous oxygen difference. During an acute bout of exercise, cardiac output increases reaching a new steady state within a few minutes.⁷ Stroke volume is lower in children than in adults, and in spite of a partial compensation by a higher heart rate, a lower cardiac output is observed at each absolute metabolic level. Arterial blood pressure (systolic and diastolic) tends to be lower in small children than in adolescents.⁷ During submaximal exercise, the higher arteriovenous oxygen difference in children compensates and helps to fulfill the oxygen demands. However, during maximal exercise, a potential handicap still exists due to the relatively lower cardiac output.

There are growth and developmental factors which determine the different responses to exercise. Maximal oxygen uptake ($\dot{V}O_2$ max), which is the highest volume of oxygen that can be consumed by the body per unit of time during maximal exercise and an index of cardiorespiratory fitness, is strongly related to lean body mass and to age. When corrected for body mass, $\dot{V}O_2$ max does not change with age in boys but it continuously declines among girls after adolescence. Oxygen cost per kilogram of body mass is higher in children during walking and running than in adults,^{9, 10} a difference that could be explained by the child's relatively energetically inefficient gait. With training, running becomes more efficient in children as reflected by a lower oxygen cost for a given task,¹¹ one of the benefits of rehabilitation. Another important factor is that the difference between the oxygen uptake needed for a given task and $\dot{V}O_2$ max, which represents the metabolic reserve, is lower in children. For these reasons children are less capable than adolescents and adults of competing in long distance races. Furthermore, the ability of children to perform anaerobic activities is lower than that of adolescents and adults.¹²

Physical conditioning can induce morphologic and functional changes in some of the parameters mentioned above that will result in an improvement of the physical working capacity of a person even if he or she is limited by illness. A discussion of those adaptations is beyond the scope of this manuscript and the interested reader is referred to recent detailed publications.⁷

Hypoactivity and Disease

Unlike most adults, children seldom require external stimuli to stay active. They will usually jump and run without special incentives, but at a lower level than that

needed to induce a conditioning effect. When we are dealing with sick children, their activity level may be decreased due to the direct effect of an illness on skeletal muscle such as muscular dystrophy or other effects related to diseases such as bronchial asthma, cystic fibrosis or diabetes mellitus. Additional factors such as parental overprotection, fear of the child or parents and lack of appropriate education about their illness can lead to hypoactivity. These factors may induce a detraining effect with a reduction in physical working capacity of the child, leading to further hypoactivity. As health care providers, it is our responsibility to avoid this vicious cycle by not recommending unnecessary limitations to exercise in the sick child. One should always be aware of the deleterious effect of exercise under certain circumstances as well as the beneficial effect of physical exercise upon the health and well-being of the child. Too often, we have seen children whose parents are aware of the presence of EIA and upon the recommendation of the physician have restricted their activities and withdrawn them from sports.

The Role of Exercise Testing in Children

Exercise testing, although less utilized in children than in adults, may be used for different purpose and in different clinical conditions. According to Bar-Or⁷ by using exercise testing we can evaluate the children's physical working capacity, which may be deficient either because of their disease or as a result of detraining. Exercise testing can help to identify a specific pathophysiological pattern in a given disease which is more likely to be present during or following the stress of exercise than at rest; for example, exercise induced asthma.

Other areas in which exercise testing has been beneficial include the diagnosis of conditions such as growth hormone deficiency¹³ or asthma in a child with atypical symptoms.¹⁴ In patients who have asthma or diabetes, the response to pre-exercise medication can be evaluated. In others, exercise testing serves to instill confidence in the child and parents about the exercise tolerance of the child and to motivate the child to increase his or her daily activity.

Asthma and Exercise

Bronchial asthma is a bronchopulmonary condition characterized by repeated episodes of bronchospasm that are reversible, spontaneously or through the use of bronchodilators. In Puerto Rico, to our knowledge, bronchial asthma is responsible for a sizable number of hospital admissions and office visits.¹⁵ The clinical expression of the condition is usually one of shortness of breath, dyspnea, tightness of the chest, cough and chest pain accompanied by wheezing. The clinical manifestations vary with the individual and the severity of illness.

For 300 years it has been recognized that exercise can induce asthma.¹⁶ The importance of this finding has now become relevant and timely with the knowledge that proper management allows athletes with asthma to compete successfully on even terms with non-asthmatic

athletes. Oded Bar-Or in his book on pediatric sports medicine,⁷ lists four points relevant to exercise and bronchial asthma as follows: a) acute exercise may trigger bronchoconstriction and an asthmatic attack, b) chronic exercise is of therapeutic value, c) exercise is an important diagnostic tool and, d) research using exercise has been conducted to investigate the pathophysiology of asthma.

Significant bronchoconstriction has been reported in more than 70 percent of asthmatics following exercise.^{17, 18, 19} If one accepts that approximately 10 percent of the population of the United States suffers from some form of asthma, then approximately 20 million people are potentially susceptible to EIA in this country alone.²⁰ In the Australian Olympic Team 8 and 10 percent of the athletes were asthmatic in 1979 and 1980 respectively.²¹ Although more than half were swimmers, others were runners. Throughout history, many olympic medalists have been asthmatics. In the last eight Olympic games, there has been at least one asthmatic medal winner.^{1, 21}

Exercise-induced asthma may be defined as a response to exercise occurring in susceptible individuals in whom there is a fall in forced expiratory volume in the first second (FEV₁) greater than 10 to 25 percent as compared to pre-exercise values.^{22, 23, 24, 25, 26} EIA can be considered a special case of bronchial hyperactivity that in itself is considered the hallmark of asthma. In EIA the stimulus to bronchoconstriction is strenuous exertion. There is only a fair correlation between the response of an asthmatic person to exercise in the laboratory and his day-to-day response to spontaneous exercise.¹⁹ In the absence of definite epidemiologic data one can only speculate about the extent of EIA in real life. However, it is conceivable that any asthmatic person may, at some time, experience EIA when his or her activity happens to be intense and of sufficient duration. Therefore, all asthmatics are potentially at risk.

When exercise first begins, there is initial bronchodilation with a fall of resistance of airflow within the lungs.²⁷ This is thought to be due to the release of endogenous catecholamines as a result of the physical stress of exercise. This is a normal response also seen in nonasthmatic individuals. In contrast to normal individuals, however, people with EIA then develop progressive airflow obstruction which generally reaches a peak in children at 4 to 8 minutes (6 to 10 in adults) after stopping exercise.²⁷ Gradual spontaneous recovery occurs over the next 20 to 60 minutes. In about 30 percent of the patients obstruction develops once more 3 to 9 hours (late phase) after exercise.^{28, 29} During the acute episode, airway resistance is elevated and airflow rates are reduced. Identification and quantification of airway obstruction is best determined by measurements of FEV₁ due to the availability, simplicity and reproducibility of the procedure.

Different mechanisms for EIA have been proposed including factors related to inhalation of dry, cool air leading to heat and water loss in the airways. Given the warm humid climate of Puerto Rico, it could be hypothesized that exercise-induced asthma would be a rare occurrence in the island. However, our experience in clinical practice suggests that EIA is not uncommon in

our environment.³⁰ Following an initial report, we have investigated 40 cases of EIA proven at our pulmonary laboratory (to be published).

In an attempt to explain the mechanisms responsible for EIA several theories have been proposed. First, it has been suggested that in some way an increase in ventilation and to a lesser extent an increase in expiratory air temperature lead to respiratory heat and water loss in the airway.³¹ This brings about osmotic changes and airway cooling throughout the mucosal surface. It has been suggested that the translation of this physiological stress to bronchoconstriction occurs through the triggering of mast cells release of chemical mediators such as histamine, bradykinin, and neutrophil chemotactic factor,³² by stimulating irritant receptors that lead to bronchoconstriction through vagal efferents or both.³³ The late phase could be explained by a second release of mediators.²⁸

One recently proposed mechanism has to do with a phenomenon called "reactive hyperemia".³⁴ When a person exercises, there is cooling of the airways by mechanisms already mentioned. Vasoconstriction of the bronchial blood vessels results from this cooling. This is a normal event in all individuals which leads to the development of a necessary thermal gradient between the airway wall and the airstream. The colder the airway the greater the gradient and the more efficient the heat exchange. When exercise stops, warming of the airway and airstream occurs. In asthmatics this occurs to a greater extent and 4 times faster than in normal individuals. It is postulated that this event is caused by a sudden rush of blood back into the airways and this may in turn cause edema, congestion of airway walls and bronchoconstriction. Whether this is caused by the release of chemical mediators remains to be determined.

In some cases, when exercise tests are conducted at intervals of 2 hours or less, a refractory period is noted during which minimal or no obstruction occurs. This refractory period is present in about 40 percent of the patients and may last up to 2 hours.^{17, 35} The probable mechanisms include desensitization of mast cells in the smooth muscle of the airways, depletion of mast cell mediators, and an increase in circulating catecholamines.³⁶

The occurrence of EIA depends upon the type of exercise performed, its intensity, duration and the atmospheric conditions under which it is carried out. The amount of respiratory heat loss during any given task is a function of the volume of air breathed. Activities such as cycling or running, which result in high ventilation rates, lead more predictably to EIA than do those that require relatively brief spurts of activity such as baseball. The ambient air temperature and humidity in which exercise is performed are also important. Swimming is particularly well tolerated by these patients probably because it is performed under warmer and more humid environmental conditions, which cause less heat loss and airway cooling. Another important factor is air pollution. Studies have shown that exercise during periods of high pollution, results in more exercise-induced asthma than during less polluted periods.³⁷

The exercise provocation test may be useful in

screening asthmatics for participation in activities, such as athletic competition. It is highly informative in the evaluation of the medications for EIA and, as a non specific challenge test, in the diagnosis of asthma in patients with atypical respiratory symptoms, or in those who have long symptomless periods.^{7, 38}

Patients with bronchial asthma who participate in exercise and sports should be restricted from activities as little as possible in order to promote optimal physical and emotional development. The best therapy for EIA is prophylactic. Beta-adrenergic drugs and disodium cromoglycate administered in aerosol prior to activity are the most effective medications for EIA.^{39, 40, 42} The use of nasal breathing and choosing a less asthmogenic activity may also be considered. The use of a drug banned by the International Olympic Committee should be avoided.⁴⁰

The therapeutic value of exercise training has been studied in asthmatic children involved in a 3-month program of general physical conditioning and instruction in breathing exercises.⁴³ A decrease in days of wheezing and in the degree of anxiousness were noted. With parental education there is an enhancement of the favorable effects of physical conditioning. Kohen⁴⁴ designed a program to teach appropriate exercises to children with asthma and to educate parents about their specific needs. As a result, school absenteeism decreased by 57 percent, emergency room visits by 70 percent, use of medication by 54 percent, and the number of attacks decreased by 70 percent.

The control of asthma in the pediatric population has improved significantly during the last 20 years. However, as stated before in this article, parental overprotection of asthmatic children may contribute to a sedentary life and poor school performance. In order to combat the above situation the Committees on Children with Disabilities and Sports Medicine of the American Academy of Pediatrics have stated that: "As a general rule, every effort should be made to minimize restrictions and invoke them only when the conditions of the child make it necessary".⁴⁵

Cystic Fibrosis and Exercise

Cystic Fibrosis (CF) is a hereditary disease of mendelian recessive transmission. The fundamental abnormality consists of the secretion of thick tenacious mucus from the exocrine glands with other pathophysiological abnormalities such as increased excretion of chlorides in the sweat and salivary glands. The major manifestations are chronic obstructive pulmonary disease and pancreatic insufficiency.

In Puerto Rico the estimated incidence is one in eight thousand live births.⁴⁶ Throughout the years the life expectancy of patients with the disease has increased to 20 to 22 years in Puerto Rico. Involvement of the chest is manifested by recurrent pulmonary infections that may cause complications such as atelectasis, hemoptysis, bronchiectasis, emphysema, pneumothorax and cor-pulmonale. As the disease progresses the vital capacity (VC) decreases, the residual volume (RV) increases and eventually the diffusing capacity is impaired.

Exercise performance of patients with CF may be affected by airway obstruction, low lung recoil, hyperreactive airways, destruction and remodeling of lung vasculature and pulmonary induced heart disease.⁸ During exertion, their maximal minute ventilation may reach 100 percent or even more of their resting maximal breathing capacity, suggesting a low ventilatory reserve.⁴⁷ Healthy children use only 60 to 70 percent of their resting maximal breathing capacity during maximal exercise. Minute ventilation is increased,⁴⁸ probably to compensate for an increase in dead space. This increase in ventilation improves endurance of their ventilatory muscles.^{47, 48}

Cystic fibrosis is associated with decreases in exercise tolerance and hemoglobin oxygen saturation, that vary according to the severity of the disease. Henke and Orenstein⁴⁹ studied 91 patients with CF and found that most of them tolerate exercise without significant desaturation. For those patients with forced expiratory volume in one second (FEV1) of less than 50 percent of their VC they recommended supervised exercise testing including oximetry. They also concluded that CF patients can perform progressive exercise tests. Cropp⁵⁰ studied 20 patients with cystic fibrosis by means of progressive exercise cycle ergometry and reported that young patients with cystic fibrosis had the ability to do physical work. The result of the study suggested that only the most debilitated patients were the ones who would experience severe arterial desaturation. Although they cautioned against unrestricted and unsupervised exercise training or inappropriate exercise, they encouraged athletic exertion for patients with mild or moderate CF.

Andreasson et al⁵¹ studied seven CF patients participating in an exercise training program. The patients were able to pursue regular physical training for years if the VC was over 50 percent of the predicted value. They concluded that physical exercise in general should be the basis for pulmonary therapy in CF. Other investigators^{52, 53} have found that a swimming program improves the clearance of mucus, reduces the airway resistance and increases the endurance of respiratory muscles.

In a hot and humid climate, such as that of Puerto Rico, the possibility of heat-related disturbances in CF patients during exertion should be high, but it is our experience that these events rarely occur. More research is needed to explain this observation. At the present time we recommend that CF patients who exercise in hot and humid weather drink water above and beyond thirst with salt supplementation.

Tuberculosis and Exercise

Pulmonary tuberculosis may temporarily affect physical fitness, but most children recover without sequelae. When these are suspected, exercise testing may be used to assess the aerobic power of the patient, thus allowing the physician to prescribe the most appropriate type of exercise training program. Valimaki and collaborators⁵⁴ studied 47 children with tuberculosis and found that the working capacity was lower than that of normal children. Pulmonary function tests indicated that the impairment was relatively mild even in the advanced cases. The investigators stated that hypoactivity may reduce venti-

latory and physical working capacity and result in a decreased functional capacity.

Other Diseases and Exercise

Many other ailments affect pulmonary function and may limit exercise performance and athletic activities. These include, interstitial lung disease, neuromuscular conditions, and nutritional problems. These and others are very well covered in Oded Bar-Or's text and are beyond the scope of this paper.⁷

Resumen: Se describe el creciente interés en el ejercicio y el deporte en Puerto Rico en general, y específicamente en nuestro Recinto Universitario de Ciencias Médicas y su Programa Pediátrico Pulmonar. Han contribuido a este creciente interés el establecimiento del Centro de Salud Deportiva y Ciencias del Ejercicio del Albergue Olímpico de Puerto Rico, además de la posibilidad de que se celebren los Juegos Olímpicos del año 2004 en Puerto Rico.

Se discuten en detalle los mecanismos fisiopatológicos mediante los cuales el pulmón de niño se enfrenta con el ejercicio y las neumopatías. Se ofrece información sobre la relación existente entre el ejercicio y el asma bronquial, fibrosis quística, y tuberculosis.

Se hace incapié en el potencial de todos los niños con enfermedad pulmonar para involucrarse en los deportes recalcando además las bondades de realizar las evaluaciones y ofrecer las recomendaciones indicadas de manera que todo niño saludable o enfermo, pueda aspirar a competir con éxito en los deportes y mejorar su calidad de vida mediante un programa adecuado de ejercicios.

Acknowledgements

The authors are indebted to Mr. Esdras Vera, Mrs. Nancy Mayol-Vera, Miss Sandra Mayol and Mrs. Rebeca Mayol-Sharp for their collaboration in the preparation of this manuscript.

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Interventional Management of Acute Myocardial Infarction

Jorge A. García-Gregory, MD, FACC

Abstract: Myocardial infarction remains the leading cause of mortality in the adults in the industrialized world.

Clinical evidence indicate that poor prognosis offer myocardial infarction related to the amount of damage or destroyed myocardium.

It is of great importance to effect immediate recanalization of the infarct related coronary artery to salvage ischemic myocardia.

Several modalities of therapy are available for the interventional management of a MI.

These include intravenous or intracoronary streptokinase; TPA and PTCA.

"Now cracks a noble heart..."
—Hamlet

Myocardial infarction remains the leading cause of mortality in adults in the industrialized world. In the United States alone there are about one million heart attacks every year. One-third of the victims die before they can reach the hospital and 25% die within the first month after the myocardial infarction.¹ Thus a cumulative mortality of about 50% occurs in the first month after the initial event. During the next six months an additional 10% will die and at one year the total mortality of those who survived the first month is about 15%. After the first year, mortality remains constant at 3 to 5% per year.

Clinical evidence indicate that poor prognoses after acute myocardial infarction relate to the amount of left ventricular myocardium damaged or destroyed with acute or previous myocardial infarctions.^{2, 3, 4} Therefore, other than preventive therapy directed at modifying risk factors for coronary artery disease, modern therapy for unstable angina or acute myocardial infarction has taken an interventional approach.^{5, 6} It is of great importance to effect immediate recanalization of the infarct-related coronary artery in an attempt to salvage ischemic myocardium and hence reduce the size of the myocardial infarction and to prevent reinfarction and sudden cardiac death after the initial acute event.

A growing body of experimental and clinical evidence support the concept that intraluminal thrombus formation and propagation is a dynamic process. The most probable initial event is rupture or fissuring of the atherosclerotic plaque. This event exposes the raw surface of the atheroma that contains potent aggregators

such as collagen and free fatty acids to circulatory blood elements. This results in a complex interaction between blood vessel wall, circulating platelets, and vasoactive mediators, all of which produce local alterations in coronary tone and restrict regional myocardial blood flow.^{7, 8}

The presence of a thrombus formed by platelet activation and aggregation superimposed on a preexisting atheroma can transform a severely but partially occluded vessel into a totally occluded one. This platelet activation in turn generates vasoactive substances that produce vascular spasm. Also intrinsic coagulation mechanisms are activated, resulting in increased fibrin production at the platelet activation site. Hence, thrombus propagation is promoted.⁹

In patients with coronary artery disease, several interesting clinical and angiographic findings demonstrate the dynamic nature of intravascular clot formation and propagation.¹⁰ At the time of cardiac catheterization patients with unstable angina have certain coronary artery lesions with a characteristic angiographic appearance when compared to matched controls with stable angina. These lesions have a rough, shaggy border and often demonstrate seemingly adherent opacities though to represent intraluminal thrombus. These lesions, designated type 2 lesions, differ in angiographic appearance from type 1 lesions seen in patients with stable angina. Type 1 lesions are smoothly contoured with well-defined edges, regardless of the severity of the stenoses.¹¹ These different angiographic lesions serve to substantiate the hypotheses that when the atherosclerotic plaque ruptures, thrombus forms and propagates at the rupture site. Clinically, these intravascular events manifest as a conversion from chronic stable angina to unstable angina or acute myocardial infarction.

It is then no surprise that in the past ten years, numerous clinical trials have reported successful interventional therapy for acute myocardial infarction using intracoronary or intravenous thrombolytic therapy.¹² An extensive review of all the intracoronary and intravenous clinical trials utilizing streptokinase provided convincing evidence that both therapies improved survival in some patients with acute myocardial infarction. To be most effective, therapy should be initiated as early as possible; and it is usually ineffective if not started within six hours of the onset of symptoms. It is generally agreed that if therapy is started within three hours of the onset of symptoms, improved global left ventricular function usually occurs. The major beneficial effect of this therapy appears to occur in patients with anterior myocardial infarction; it showed little or no benefit for those with inferior myocardial infarction.¹³

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The GISSI trial of intravenous streptokinase carried out in over 11,000 patients showed a significant sustained reduction in mortality if intravenous streptokinase was administered within the first three hours after the onset of myocardial infarction.^{14, 15}

Substantial clinical experience has now been obtained with the use of intravenously injected tissue plasminogen activator produced by recombinant techniques (rt-PA) in early treatment of acute myocardial infarction. The two largest, prospective randomized, double blind trials with rt-PA, i.e., the TIMI trial and the European Cooperative trial, are concordant and compatible with smaller studies with native t-PA or rt-PA. Several important features of rt-PA have been shown in the different trials.¹⁶ Intravenous rt-PA elicits recanalization promptly in over 70% of patients—a success rate compatible with that documented with maximal doses of intracoronary streptokinase. rt-PA also appears to deplete circulating fibrinogen and elevate circulating fibrinogen degradation products much less than does streptokinase. Bleeding associated with rt-PA generally involved large doses of heparin and was generally confined to vascular access sites and most of the time was readily manageable. Intracranial bleeding was reported in a low percentage of patients. Rt-PA administration early in the course of myocardial infarction was associated with remarkably low mortality in patients with documented acute transmural infarction.^{16, 17}

Several other thrombolytic agents are now in clinical trials. These include single chain prourokinase plasminogen activator (scuPA) and anisoylated plasminogen streptokinase activator complex (APSAC).¹⁸

Despite the documented salutatory effect of decreased mortality, improved left ventricular function and limitation of infarct size, reocclusion of the vessel involved and residual coronary artery stenoses represent bothersome problems in patients receiving thrombolytic therapy alone. These findings have led investigators to employ a variety of strategies using (percutaneous transluminal coronary angioplasty (PTCA)).¹⁹

With these limitations in mind some cardiologists have advocated the use of PTCA alone or in combination with thrombolysis in patient with acute myocardial infarction. Patency rates of 85-90% make PTCA the most successful means of acutely restoring full arterial patency.²⁰

Results of several trials have shown that the clinical outcome of patients who undergo elective angioplasty does not differ significantly from those who receive immediated angioplasty following thrombolytic therapy.²¹ Rather than coronary angioplasty the key determinant of in-hospital clinical course in the thrombolysis and angioplasty in myocardial infarction (TAMI) trial and the long-term prognoses in other reperfusion studies appear to be infarct vessel patency.²² However, approximately 25% of patients with failed rt-PA therapy might benefit from angioplasty-induced reperfusion. In the TAMI trial the investigators termed this use of angioplasty as "salvage" because it is a method of achieving recanalization in the setting of failed lytic therapy. Left ventricular function was not improved by "salvaged angioplasty," but there was a very low six-month-out-of-hospital mortality in the group of 85 patients who

underwent immediately angioplasty after unsuccessful rt-PA therapy.

A practical approach can be extrapolated from the TAMI trial results: The aggressive approach of emergency cardiac catheterization, with coronary angioplasty or bypass surgery as needed may be especially appropriate in high risk patients. This group includes patients with cardiogenic shock, extensive anterior infarction or prior remote transmural infarction. On the other hand, patients with low risk infarction may well be suited for thrombolytic therapy alone with predischage exercise testing or screening coronary arteriogram.²⁴

The use of PTCA alone without thrombolysis in the acute myocardial infarction has been advocated by several groups.^{20, 25, 26}

PTCA in the setting of acute myocardial infarction carries an 85-90% recanalization rate contrary to initial success of 75% or less by thrombolytic therapy alone. In most patients who received thrombolytic therapy there appears to be the presence of high grade residual stenoses even after restoration of flow. Angioplasty alone appears to be a more complete procedure with low residual stenoses. The acute reocclusion rate in primary PTCA is much lower than with thrombolytic therapy alone. Waller, et al²⁷ showed a significant hemorrhage into ischemic myocardium in patients who underwent thrombolysis alone or in combination with PTCA. He felt that this could have a deleterious effect in ultimate muscle recovery. When PTCA was used alone, there was no evidence of hemorrhage into the ischemic myocardium.

Several studies^{20, 24} have shown a significant improvement in ejection fraction (EF) at three months, especially when the PTCA was performed under three hours from the initiation of symptoms.

Initial angioplasty can be of value for the treatment of patients in whom systemic thrombolysis is contraindicated, e.g., those with recent surgery or stroke, active peptic ulcer disease, or severe systemic hypertension. Moreover, it does not preclude the administration of low-dose intracoronary thrombolysis if residual thrombus or embolized material is seen.

The disadvantage of initial emergency PTCA are readily apparent. It requires a well equipped 24-hour cardiac catheterization laboratory and very highly trained personnel on call 24 hours a day. Of the 5,716 hospitals in the United States only 12.7% are equipped to handle emergency PTCA.²³

Other arguments have been made that primary angioplasty is an extremely costly procedure compared to thrombolytic therapy. However, the cost of some of the newer thrombolytic drugs is comparable to the cost of the physician fee for the emergency angioplasty. Both groups of patients usually require catheterization. In the case of patients receiving thrombolytic therapy alone, two catheterizations are may many times necessary. One catheterization is usually performed acutely to assess the extent of disease and the second is necessary at a later date in the hospital course if angioplasty is contemplated. When PTCA alone is performed initially, only one catheterization is usually needed.

In conclusion, there seems to be a place for the different available modalities of interventional therapy in

the acute myocardial infarction setting. It is possible that more hospitals in the United States will have the capability of performing emergency PTCA; however, the imminent development of safer, more effective and more available thrombolytic agents will enhance the ability of treating the acute myocardial infarction at a very early stage. Still, the most important development will be the generalization of preventive modalities coupled with early treatment of coronary artery disease.

Resumen: El infarto del miocardio es la causa de muerte más importante en el mundo industrializado.

Hay mucha evidencia clínica que el pronóstico del infarto está relacionado a la cantidad de miocardio que está afectado.

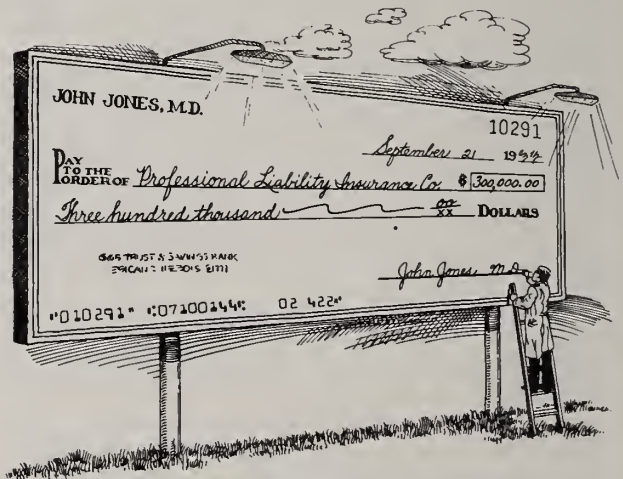
Lo más importante es intervenir temprano en el curso del infarto del miocardio. Ciertas modalidades incluyen trombolisis con estreptokinasa, TPA, y angioplastia inmediata sin trombolisis.

Todos éstos tratamientos tienen su lugar en el manejo agresivo de pacientes con infartos.

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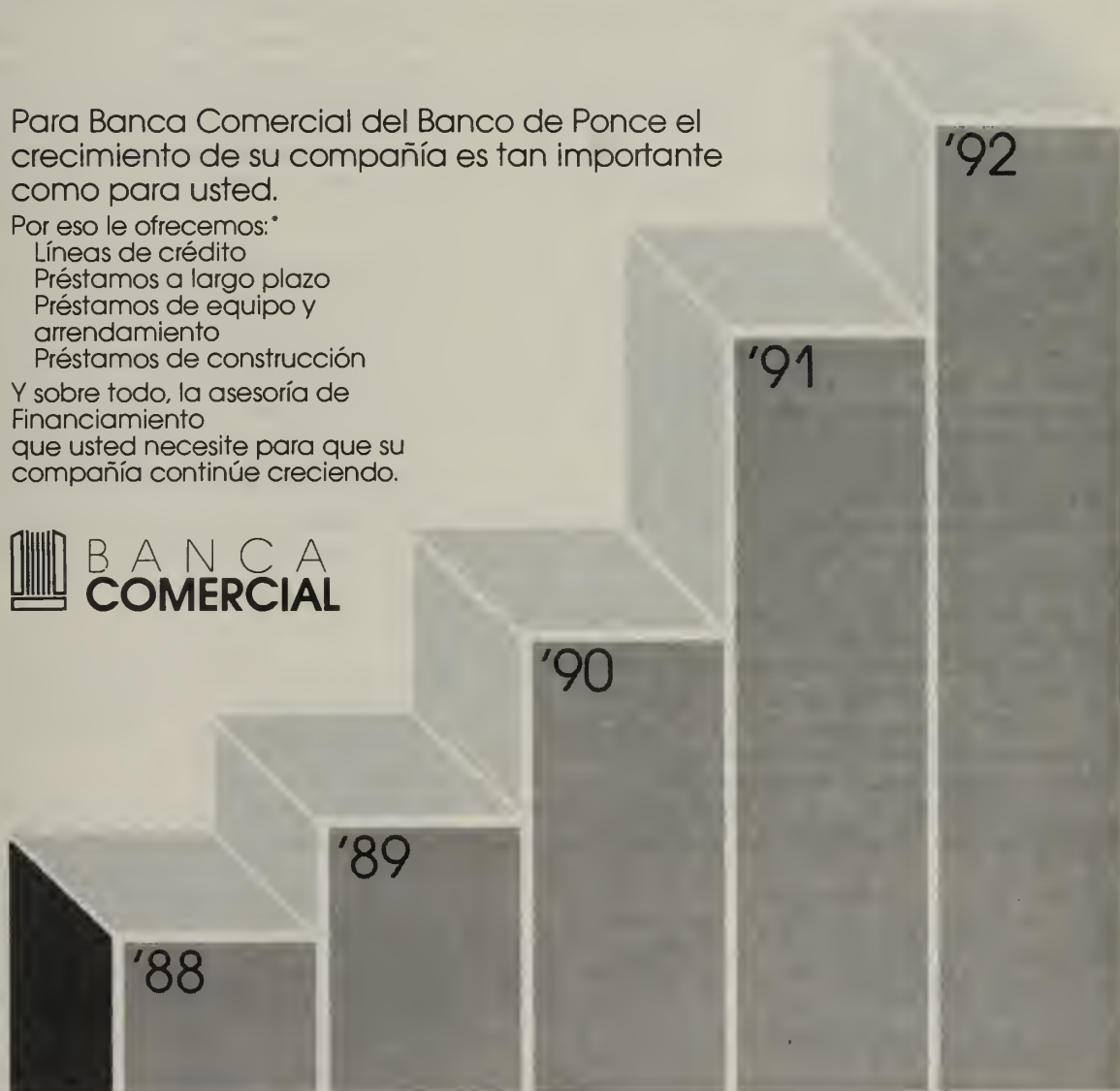
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*** 12th Anniversary Scientific Program ***

Seminar in Cardiology, Cardiovascular Surgery and Intensive Care Medicine

October 28, 29 and 30, 1988

San Pablo Hospital Amphitheater

Friday, October 28 (PM)

7:00	Registration and Welcome Cocktail	
8:00	Introduction	Dr. Rafael Brito
8:15	Muscle Physiology and Rehabilitation: Cardiovascular Response to Exercise	Dr. Walter Frontera
8:45	Pathogenesis of Arteriosclerosis	Dr. Ramzy S. Cotran
9:30	Cardiovascular Surgery Historical Review	Dr. Ernest Traad

Saturday, October 29 (AM)

Moderator: Dr. Rafael Brito

8:00	Registration Coffee and Pastries	
9:00	Thromboembolic Agents: Management and Risks	Dr. Juan M. Igartúa
9:20	Controversies in the Management of Acute Myocardial Infarction	Dr. George García Gregory

9:40	Reoperative Cardiac Surgery: Indications and Expected Results	Dr. Ernest Traad
10:00	Surgical Management of Tachyarrhythmia	Dr. Isaac Gielshinsky
10:30	Break	
10:45	Frontiers in Cardiovascular Anesthesia	Dr. Marcos Zuazo
11:05	PTCA vs Coronary Artery Disease Surgery	Dr. Isaac Gielshinsky
11:35	Surgical Management of Complications in Acute Myocardial Infarction	Dr. Manuel Martínez
11:55	Mitral Valve Repair Surgery	Dr. David Cohen
12:30	Questions and Answers	
12:45	Lunch	

Saturday, October 29 (PM)

Moderator: Dr. Manuel Lores

1:45	Heart Transplantation	Dr. David Cohen
2:15	Transfusion Requirement in Cardiac Surgery	Dr. John D. Milam
2:45	Post Operative Management in Cardiac Surgery	Dr. James T. Gallagher
3:15	Break	
3:30	Integrity of Conduction System After Heart Transplantation	Dr. J. Villafañe, Jr.
3:50	Lung Physiology and Ultra High Frequency Ventilation	Dr. James T. Gallagher
4:20	Complications in the Critical Care Unit	Dr. Víctor Salcedo
4:50	Intraoperative Blood Salvage	Dr. John D. Milam
5:20	Pharmacologic Therapy During Mechanical Ventilation	Dr. James T. Gallagher
5:40	Questions and Answers	

Sunday, October 30 (AM)

Moderator: Dr. G. García-Gregory

8:00	Registration Coffee and Pastries	
9:00	Rheumatic Heart Disease Revisited	Dr. Arturo Medina Ruiz
9:20	Kawasaki Disease Cardiovascular Complications	Dr. Rafael Villavicencio
9:50	Interventional Cardiac Catheterization in Children	Dr. J. Villafañe, Jr.
10:20	Surgical Management of Cardiac Arrhythmias in Children	Dr. Fred Crawford
10:50	Break	
11:00	Pathological Considerations in Endomyocardial Biopsies	Dr. I. Cohen
11:30	Cardiovascular Applications Laser Angioplasty	Dr. Christopher White

Sunday, October 30 (PM)

12:00	Frontiers of Shock, Pharmacology and Metabolism	Dr. Marcos Zuazo
12:30	Current Devices in Cardiac Prosthesis	Dr. Fred Crawford
1:00	Questions and Answers	
1:15	Anniversary Lunch	

Osteoporosis: A Review

Ismael Toro Grajales, MD

Abstract: The incidence of osteoporosis increases with age and fractures attributed to osteoporosis are a source of significant morbidity and mortality in the elderly. Presently, diagnosis of this condition and patient response to the therapeutic strategy can be determined by means of bone density measurements and biochemical blood tests. Possible treatments include estrogen replacement, calcium, vitamin D, calcitonin, and promising new regimens such as coherence therapy in which we pursue to uncouple the phases of bone formation and resorption and thus, open a new frontier in the effective and safe prevention of the sequelae for this disorder.

An estimated 1.3 million fractures each year in the U.S.A. are attributable to osteoporosis. Of these, approximately 250,000 are hip fractures with an excess mortality of 15 percent in the first three months after injury and up to 34% after six months. Half of those who do survive never recover normal function and total costs to the U.S.A. are estimated at 7 to 10 billion dollars in direct and indirect expenses.¹ Present epidemiological research in Puerto Rico suggests that the significance of this disorder is more than previously suspected as a source of disability and mortality particularly in our elder population.

Classification

The most common form of primary osteoporosis is involutional osteoporosis. It begins in middle age and results predominantly in the loss of trabecular bone (10 to 15% per decade). The female to male ratio is 6:2 and it is also commonly known as postmenopausal or type I osteoporosis. It affects a variable subset of women (10 to 15%) within 20 years of menopause and is characterized by vertebral and wrist fractures.

Type II affects both women and men over the age of 70 years. I has a female/male ratio of 2:1. It is multifactorial in origin and, although believed to be secondary to decreased production by the kidney of Vit. D₃, it could also be effected by aging changes such as: decreased bone formation activity, decreased calcium absorption in the gut, age related hormonal changes, decreased calcium production, and/or increased circulating levels of parathyroid hormone (PTH). It causes an estimated mineral loss of 6 to 8% in the trabecular and 3 to 5% loss in the cortical compartment per 10 year period.

Diagnosis

A fundamental responsibility of the clinician in assessing patients suspected of having the condition is the

determination of risk factors present and the exclusion of the various causes of secondary osteoporosis as shown in tables I and II for risk factors and secondary osteoporosis listings.

Presently this diagnosis is identified when a hip or spinal fracture occurs after minimal, usually home-based, trauma. It is estimated in the U.S.A that by 65 years of age, 50 percent of females will develop at least one type of osteoporosis-related fracture and this risk increases proportionately with aging.

Table I

Risk Factors for Primary Osteoporosis

- Increasing age
- Race (Caucasian, Oriental)
- Female sex
- Positive family history of osteoporosis
- Estrogen deficiency
- Small-boned and/or thin build
- Chronic low calcium intake
- 2 alcoholic drinks / day
- Lack of exercise
- Cigarette smoking
- Nulliparity
- Chronic use of steroids
- Excessive caffeine consumption

Table II

Causes of Secondary Osteoporosis

Endocrine disorders	Malignancies
Cushing's disease	Leukemia
Thyrotoxicosis	Lymphoma
Hypogonadism	Multiple myeloma
Hyperparathyroidism	Systemic mastocytosis
Hyperprolactinemia	Ectopic ACTH syndrome
Acromegaly	Ectopic parathyroid hormone syndrome
Diabetes	
Gastrointestinal disorders	Drugs
Cirrhosis	Glucocorticoids
Alactasia	Dilantin
Subtotal gastrectomy	Heparin
Malabsorption syndrome	Alcohol
Chronic obstructive jaundice	
Severe malnutrition	
Anorexia nervosa	
Genetic abnormalities	Other
Marfan syndrome	Renal failure
Ehlers-Danlos syndrome	Vit. K deficiency
Osteogenesis imperfecta	
Homocystinuria	

In order to permit earlier diagnosis and increase the effectiveness of treatment, a new working definition of osteoporosis is deemed necessary. One which permits recognition of patients at risk for osteoporosis-related fractures prior to the occurrence of such events. By utilizing the concepts of a fracture threshold and bone mass, we can identify patients at risk who have not yet suffered a fracture.

In Puerto Rico we have various diagnostic resources. In particular, photon absorptiometry is non-invasive, highly sensitive for bone losses of 2 to 3 percent per year and of acceptable cost (40-75 dollars). It permits adequate screening, gradation and follow-up of the effectiveness of treatment for this disorder. By plain roentgenography, over 50 percent of bone mass could have been lost prior to detection of the osteoporotic process; a luxury which is not permissible when our therapy is expected, on a long term basis, to halt bone density loss rather than replace the losses that have already taken place by the time of diagnosis.

Although Quantified Computed Tomography (QCT) could also be used to determine bone mass, I disfavor it for various reasons: a) higher costs and lack of availability of QCT, b) less precision and, thus, results are less reproducible, c) much higher radiation exposure, d) more discomfort to patient, and e) it does not permit visualization of other significant skeletal sites, such as direct assessment of the femoral neck.² Unfortunately present biochemical screening tests have low sensitivity or specificity for this disorder. None the less, they are still useful in the exclusion of other metabolic disorders and in the identification of patients in high turnover states. In addition to the ones commonly used, the ratio of spot calcium to creatinine is increased (>0.16) and the levels of bone GLA-protein (an osteoblastic activity marker) are raised in high turnover states.

Although no screening test by itself has been able to predict the occurrence of fractures I believe that the appropriate combination of the present resources can provide clinically useful data for decision making at the individual patient care level.

Management

Once the diagnosis has been made and degree of loss established, we can plan a rational approach to therapy permitting us to curtail the predicted 3 to 5 percent of bone density loss per year in rapid turnover cases and providing for significant reduction in fracture risks. Bone density studies will provide data to guide us in determining medication effectiveness and the need to modify our management strategy.

Estrogen replacement

The benefits of estrogen replacement have been well established in the medical literature particularly for the peri-menopausal years. It is only recently that clinical trials with women over 70 years of age have demonstrated benefits of estrogen therapy in advanced age.³ Even at this age, I do consider an older woman a candidate for estrogen therapy if there are no other contraindications and she is in good functional state and activity level. I use

conjugated estrogens at a dose of 0.625 mg on days 1 thru 25 of each month. To minimize risks of endometrial carcinoma 5 to 10 mgr. of medroxyprogesterone are added from day 15 thru 25 of the cycle. If withdrawal bleeding is a problem some researchers are utilizing the progestin dose throughout the complete cycle decreasing the chances of bleeding to 10%. The safety of this measure is yet to be determined.

Calcium

Older individuals require a higher calcium intake in order to achieve a positive calcium balance. Their daily elemental calcium intake should be between 1,200 and 1,500 mg per day. If supplementation is needed, we prefer calcium carbonate (40 percent elemental calcium) which should be taken with meals to maximize its absorption. Calcium supplementation alone is not adequate in the prevention or treatment of osteoporosis for the majority of patients since at best it seems to suppress cortical bone loss only.⁴

Vitamin D

Vitamin D promotes calcium absorption in the gut and may help to achieve a positive calcium balance. I usually supplement my patients diet with 800 IU per day of vitamin D, but we must be aware that exposure to sunlight is the basic source of this nutrient. It is estimated that 30 minutes of sunlight each day provides the needed requirements of vitamin D. A baseline blood level of 25-hydroxycholecalciferol could be helpful to sustain a suspected diagnosis of osteomalacia, but in these cases I suggest quantitative bone histology to document the diagnosis if still in doubt.

Newer Therapeutic Modalities

A knowledge of the fundamentals of bone remodeling is needed to understand the mechanisms of action of newer therapeutic modalities. Bone contains two major cell types: osteoblasts, which lay bone down, and osteoclasts, which resorb bone. These cell types are intimately related. They form cell packets known as basic multicellular units (BMU's) within which their activities of resorption and formation are coupled and controlled by chemical signals.⁵ Within a given area of bone, there are certain number of BMU's. At a given time the osteoblasts of one BMU may be laying down bone while in a neighboring BMU the osteoclasts are resorbing bone and, in yet another, both cell types are dormant.

Aside from the concept of this chemical coupling, it is important to understand the sequence of events. The osteoclasts are activated first probably by P.T.H. These cells then release one or more chemical messengers that activate the osteoblasts in the same BMU which begin to form bone at the same rate at which it is being resorbed. A period of quiescence follows in that BMU. The entire cycle takes approximately 90 days.

Newer therapeutic modalities attempt one of three effects: stimulate osteoblasts, inhibit osteoclasts, or a combined effect resulting in a decoupling of the BMU with resultant increased bone formation and a decrease in bone resorption.^{6, 7}

Calcitonin

Calcitonin directly inhibits osteoclast activity causing an average increase of 8 percent in bone mass during the first year, which then drops as low as 2 percent increases per year on the second year. The calcitonin responsive group is estimated at 50 to 60 percent of the population.⁸ The expense and inconvenience of parenteral administration make this a drug to consider mainly when estrogen treatment is not feasible and patient's osteoporotic risk is high. It is given as 100MRC units subcutaneously at least three times per week. Its effectiveness can be increased by the administration of phosphates. It also provides an analgesic effect which is ascribed to elevations in circulating beta-endorphin levels.

Fluoride

Fluoride works by directly stimulating osteoblastic activity and in clinical trials has yielded an average first year increase of 8 percent in approximately 50 percent of patients.⁹

Since it does not result in an uncoupling of the osteoclastic and osteoblastic activity, its long-term efficacy in sustaining increments of bone density is unknown. Gastrointestinal discomfort and plantar fasciitis occur in approximately 40 percent of patients at the recommended doses of 40 to 80 mg per day. Some studies have revealed no effect on the incidence of hip fractures after three years of therapy. Its use is limited to some patients with severe vertebral osteoporosis.⁷

Androgen

Androgen decreases bone resorption and may also increase bone formation. The first year average increase in bone mass is estimated at 4 to 5 percent.¹⁰ This treatment modality is considered particularly for hypogonadal men and potentially in patients with glucocorticoid mediated osteoporosis. It is rarely used in females due to masculinization effects, adverse effects on plasma lipoproteins/liver function, and the development of hepatic tumors.⁷

Coherence Therapy

This initiative is supported by the belief that long-term bone buildup by pharmacologic manipulation is dependent on (a) uncoupling the bone formation and resorption processes within the BMU, and (b) synchronization of BMU's so that all would be either in the resorption or formation phase simultaneously. Two regimens available experimentally seem to accomplish the goal of chemically uncoupling bone formation and resorption: ADFR and pulse-dose therapy.

The safety and long-term efficacy of these interventions are presently limited to a few centers which have developed the expertise necessary for proper administration and supervision of care. By 1990 we should have data of a 42-month multicenter trial presently under way to clarify these and other issues related to coherence therapy.

Conclusion

The primary care physician is in a unique position to have a positive impact in reducing the incidence of osteoporotic fractures and the morbidity and mortality associated with such fractures. Our fundamental objective is to identify patients at risk early, before a fracture occurs. Referral to a consultation diagnostic facility for bone mass measurement is appropriate to confirm the disease and in patients with established fractures who are starting pharmacological therapy intended to increase bone mass. The diagnostic facility will help you monitor the patient's response to such therapy. If initial pharmacologic management is shown ineffective, strong consideration should be given to more active pharmacological therapy.

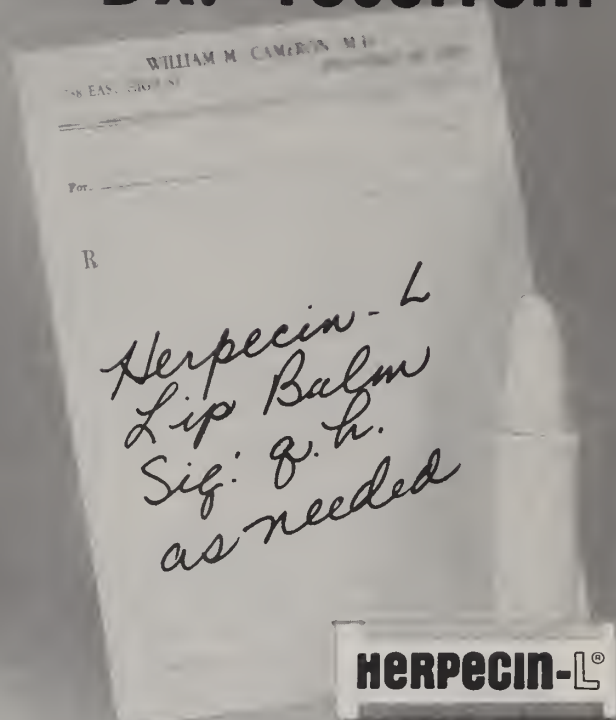
It is fundamental that in every patient diagnosed with osteoporosis a thorough evaluation be performed to rule out secondary causes of the condition and minimize future risks.

Resumen: La incidencia de osteoporosis aumenta con la edad y las fracturas asociadas con este proceso son una fuente significativa de morbilidad y de mortalidad particularmente para la población envejeciente del país. Al presente podemos corroborar, no solo el diagnóstico, sino también la efectividad de nuestra intervención terapéutica a través de marcadores bioquímicos en sangre y orina al igual que con mediciones directas de densidad mineral con el absorbiómetro de fotón. Las alternativas terapéuticas incluyen: el uso de estrógeno, calcio, vitamina D y calcitonina. También disponemos de nuevos regímenes experimentales que persiguen disociar las fases de formación y reabsorción ósea explorando así una nueva frontera en alternativas para la prevención efectiva de las serias consecuencias de esta enfermedad.

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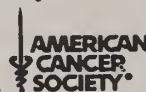
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ARTICULOS ESPECIALES

Suspensión de Privilegios Médicos en la Facultad Médica de un Hospital Privado o de la Comunidad

Milton L. Cruz, BA, JD, LLM

Resumen: En este artículo el autor da un breve resumen de la forma en que las cortes de los estados de los Estados Unidos de Norteamérica confrontan el "issue" de suspensión de privilegios médicos en la facultad médica de un hospital privado o de la comunidad. En segundo lugar, el autor analiza el tratamiento de este tema por el Tribunal Supremo de Puerto Rico, según expuesto en el caso de *Hernández v. Asoc. Hosp. del Maestro*. Finalmente, se dan sugerencias para evitar posible responsabilidad legal en este tipo de casos.

El propósito de este artículo es el de exponer la forma en que el Tribunal Supremo de Puerto Rico confronta el tema de suspensión de privilegios médicos en la facultad médica de un hospital privado o de la comunidad. Primeramente, se expondrá brevemente la manera en que las cortes de los Estados Unidos de Norteamérica confrontan este "issue". Luego se analizará el caso de *Hernández v. Asoc. Hosp. del Maestro*,¹ decidido por el Tribunal Supremo de Puerto Rico y que trata sobre este tema. Finalmente, se darán sugerencias para evitar posible responsabilidad legal en este tipo de casos.

Como regla general los médicos no son empleados de la institución hospitalaria en donde tienen privilegios. Aquellos que son empleados del hospital donde a su vez tienen privilegios están en una relación legal de patrono-empleado. Esta relación de patrono-empleado le da unas garantías mínimas al médico. El patrono, bajo la teoría de "*respondeant superior*"² es responsable por los actos negligentes del médico-empleado. Debido a esta responsabilidad, el hospital, para reducir este riesgo, despidió o suspende al médico-empleado cuando su conducta lo justifica.

En el caso de un médico que no es empleado de la institución, no aplica la teoría de "*respondeant superior*" antes mencionada. Sin embargo, a partir del famoso caso de *Darling v. Charleston Community Memorial Hospital*,³

se le empezó a imponer "responsabilidad corporativa" a los hospitales por las actuaciones de los miembros de la facultad. Esto prácticamente puso al hospital con la misma responsabilidad frente a un médico no empleado como si fuera un empleado. Esta posible responsabilidad legal hace que los hospitales, en su buen juicio, *niegen, revoquen o suspendan* a aquellos médicos no empleados que no cumplen con las normas razonables establecidas por la institución.

Estados Unidos de Norteamérica

Los derechos de los médicos en situaciones de suspensión de privilegios varía dependiendo de la ley particular en la jurisdicción en donde ocurra la suspensión. Varias jurisdicciones rehusan, como regla general, permitirle a los médicos que demanden al hospital que los suspendió. Aún en estas jurisdicciones el médico podría tener un remedio legal si el hospital al suspenderlo ha violado su reglamento interno, ya que éste podría considerarse un contrato.⁴

Los tribunales de los diferentes estados de los Estados Unidos que permiten revisión judicial de las suspensiones de los médicos se basan en dos teorías. La primera es la "teoría fiduciaria" en donde se enfatiza la función pública de los hospitales.⁵ La segunda está basada en el llamado "common law duty of fair procedure" basada en el debido proceso de ley del derecho común.⁶

Puerto Rico

El Tribunal Supremo de Puerto Rico solamente ha tenido la oportunidad de discutir el tema de suspensión de privilegios médicos en el caso de *Hernández v. Asoc. Hosp. del Maestro*⁷ decidido el 31 de mayo de 1977. El Comité Ejecutivo de la Facultad Médica del Hospital recomendó la suspensión de uno de los miembros de la Facultad Médica. El doctor afectado utilizó su derecho de solicitar una vista y reconsideración de la decisión ante el Comité de Revisión Judicial. Dicho Comité de Revisión Judicial determinó lo siguiente:

(1) El querellado no fue lo suficientemente diligente para conseguir quien le relevara en un turno de guardia de emergencia en 14 de noviembre de 1974; (2) El expediente clínico de una de sus pacientes hospitalizada en febrero de 1975 resultaba inadecuado por no reflejar la gravedad de su estado ni el tratamiento recibido; (3) los expedientes médicos del querellado durante el último año reflejaban una manifiesta falta de diligencia y esmero de su parte.⁸

A pesar de lo anterior, el Comité de Revisión Judicial recomendó que se le diera al doctor afectado un nombramiento de carácter probatorio de un año. El doctor aceptó dicho nombramiento. Posteriormente, se le comunicó al doctor que la Junta de Directores no había aceptado la recomendación del Comité de Revisión Judicial y que de inmediato se le suspendían todos sus privilegios.⁹ El doctor suspendido demandó al Hospital del Maestro solicitando del Tribunal una orden de interdicto para que el hospital lo restituyera como miembro de la Facultad Médica del Hospital. El doctor acudió al Tribunal Superior sin antes haber agotado el procedimiento de apelación y/o reconsideración establecido en el Reglamento del Hospital. Dicho Reglamento le concedía al doctor afectado oportunidad de solicitar reconsideración y la celebración de una vista.¹⁰ El doctor solicitó vista, pero acudió al Tribunal antes de la celebración de la misma.

El Tribunal Superior expidió el interdicto ordenando la reinstalación de los privilegios del doctor, pero el Tribunal Supremo modificó la orden de interdicto y ordenó que se tenían que agotar los procedimientos establecidos en el Reglamento del Hospital —reconsideración y vista— antes de poder acudir a los tribunales. En adición, el Tribunal Supremo ordenó que se limitara la vigencia del doctor en el hospital como miembro provisional, ya que entre las razones para la suspensión sumaria que provee el Reglamento del Hospital no se encontraban enmarcadas las actuaciones del doctor afectado.¹¹

De la opinión del Tribunal Supremo, se desprenden una serie de normas generales, las que los hospitales y los médicos deben tener en mente en situaciones de suspensión o revocación de privilegios, a saber:

1. Los médicos afectados tienen que agotar los procedimientos internos del hospital antes de acudir a los tribunales.
2. Los tribunales darán gran deferencia a las normas procesales de los Reglamentos de un hospital si las mismas cumplen con las garantías mínimas del debido proceso de ley.
3. Las normas adoptadas por un hospital serán respetadas por los tribunales a menos que sean muy vagas, subjetivas o caprichosas.
4. Un hospital privado puede suspender, retirar o limitar privilegios de un médico, pero no de forma irrazonable, caprichosa o arbitraria.
5. Médicos excluidos en forma irrazonable de la Facultad Médica pueden ser repuestos.

6. El médico tiene derecho a una audiencia para presentar prueba a menos que "su continua presencia en el hospital constituyera una seria e inmediata amenaza."¹²

Lo anterior nos indica que en Puerto Rico los tribunales dan gran deferencia a las determinaciones de los hospitales y el contenido de sus Reglamentos a menos que a) "...la reglamentación no satisfaga los requisitos mínimos del debido proceso de ley..." y b) "sus determinaciones sustantivas sean arbitrarias, caprichosas o irrazonables."¹³

Recomendaciones

La mejor manera en que los hospitales pueden reducir los riesgos de responsabilidad es manteniendo un Reglamento que garantice el debido proceso de ley de los médicos afectados. Como nos indica el caso de *Hernández*, al igual que varios casos federales,¹⁴ como un mínimo el debido proceso de ley incluye una notificación y oportunidad de ser oído. Dependiendo del caso particular, las garantías procesales varían. Un caso de mera amonestación generalmente no requiere tantas garantías procesales como un caso de total suspensión de privilegios. Sin embargo, mientras más garantías procesales se le provean al médico afectado en mejor posición está el hospital si el médico cuestionara la actuación del hospital.

La ley federal "Health Care Quality Improvement Act of 1986."¹⁵ que entre otras cosas, provee un mecanismo para que los comités de revisión de pares obtengan inmunidad de demandas bajo ciertas leyes, contiene unas normas sobre el debido proceso de ley, entre las que incluye: a) notificación de la acción disciplinaria propuesta, b) notificación del lugar, hora y fecha de la vista de por lo menos 30 días, c) vista ante un árbitro aceptable a todas las partes, un oficial de vistas o una persona que no compita directamente económicamente con el médico afectado y d) permitir asesoramiento legal.¹⁶ Este tipo de garantías, entre otras, fortalecen la posición de la institución, de los médicos que evaluaron el caso del médico afectado, y le garantizan un resultado más justo al médico. Los hospitales deben estar consientes de esta ley federal.¹⁷

En conclusión, los hospitales deben tener un Reglamento, el cual deberá ser revisado regularmente para que cumpla con las exigencias del ordenamiento jurídico de Puerto Rico, los Estados Unidos y con las normas establecidas por las agencias que acreditan hospitales. Dicho Reglamento tiene que cumplir con las garantías procesales, y las normas sustantivas de la institución tiene que ser razonables.

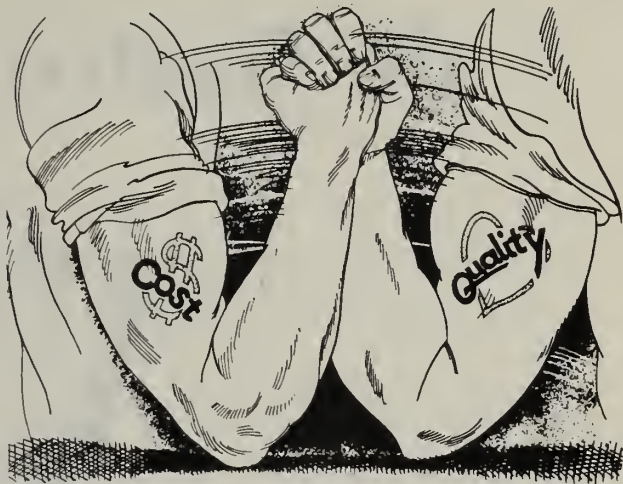
Summary: In this article the author, first of all, gives a brief summary of the way in which the courts of the United States of America deal with the issue of the suspension of medical staff privileges at a private or community hospital. Second, the author analyzes the treatment of this issue by the Supreme Court of Puerto Rico as expressed in the case of *Hernández v. Asoc. Hosp. del Maestro*. Finally, the author gives suggestions and recommendations that hospitals may follow to avoid possible legal responsibility in this type of cases.

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8. *Ibid.* página 74.
9. *Ibid.* página 75 y 76
10. *Ibid.* página 76.
11. *Ibid.* página 79 y 82
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13. *Ibid.* página 81. Para un análisis extenso del debido proceso de ley y los derechos de los médicos, véase, entre otros, Cruz, M.; The Duty of Fair Procedure and the Hospital Medical Staff: Possible Extension in Order to Protect Private Sector Employee; Capital University Law Review 1986; 16:59-86
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15. 42 U.S.C. Sec. 11101 *et. seq.*
16. Federal law offers protection for peer review: In: Hospitals, 1988; Vol. 62 No. 13:46-48, American Hospital Publishing, Inc. 42 U.S.C. Sec. 11101 *et. seq.* Los hospitales participantes de los Programas de Medicare y Medicaid también deben estar consientes de la ley federal "Medicare and Medicaid Patient and Program Protection Act", ley Pública Número 100-93.
17. En Puerto Rico la Ley Número 3 del 30 de diciembre de 1986, 20 LPRA Sec. 52a provee inmunidad a los miembros de los Comités de Garantía de Calidad en "acciones de daños y perjuicios por cualquier acto, procedimiento o testimonio realizado o prestado como parte de las funciones del Comité de Garantía de Calidad, siempre y cuando no actúen intencionalmente y a sabiendas del daño que razonablemente se puede ocasionar." 20 LPRA Sec. 52a(6).

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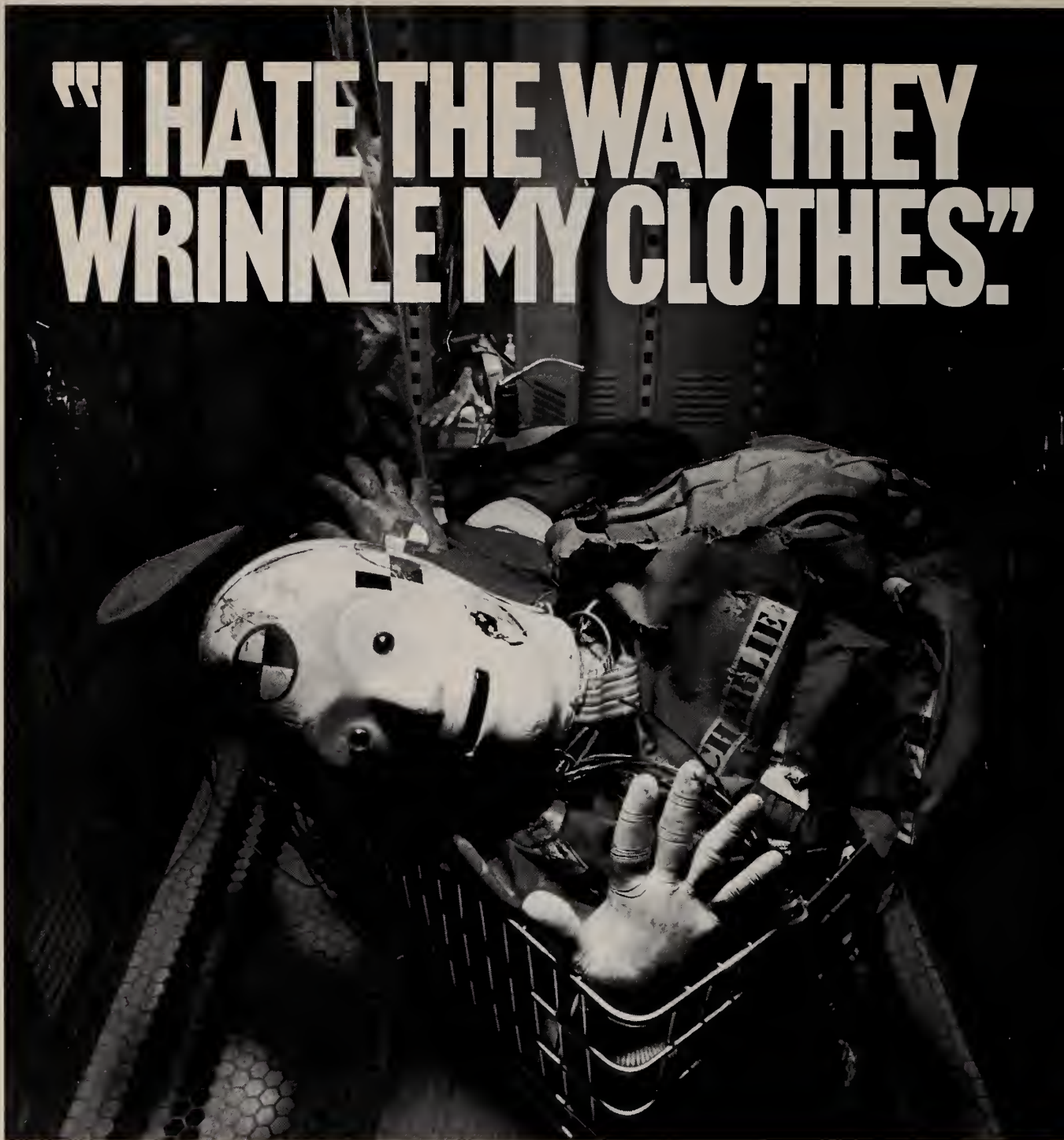
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Estrategias Básicas de Investigación Clínica para el Médico Primario

Ilia E. Zayas-Toro, MD, DABFP

Resumen: La investigación clínica es analizada desde la perspectiva de la medicina primaria. Debido a que el médico primario es el portal de entrada en nuestro sistema de salud, el mismo está expuesto a las diferentes etapas en que puede presentarse una enfermedad. Hecho que le permitirá seleccionar una muestra más representativa de la población que padece de una determinada enfermedad. En este artículo se hace una revisión de las estrategias básicas de investigación. El entendimiento de estas metodologías investigativas le proveerán al médico los instrumentos necesarios para involucrarse en la investigación clínica y evaluar críticamente la literatura médica existente.

La investigación científica es un proceso en el cual se hacen observaciones precisas de las relaciones entre los fenómenos naturales. Se formulan hipótesis que explican estas relaciones y se prueban frente a la experiencia. Esto se hace a través del análisis de unos datos que han sido coleccionados de manera sistematizada. La mayoría de la investigación médica ha sido en el área de las ciencias básicas. La investigación en el área clínica ha recibido menos énfasis por parte de los investigadores. Esta investigación clínica usualmente se hace en centros de cuidado médico especializado o centros universitarios.

Los estudios clásicos de White, Williams y Greensburg en 1961,¹ demostraron que de cada 1,000 personas de la población de alto riesgo en una comunidad, solamente el uno por ciento será hospitalizado o referido a centros médicos universitarios para tratamiento. Analizando este estudio concluimos que los pacientes tratados en un centro universitario representan una muestra atípica de enfermedades que ocurren en las comunidades, ya que usualmente son referidos a estos centros los casos más severos. Sin embargo, esta muestra seleccionada de pacientes ha servido predominantemente como la población de estudio en la investigación clínica.

Es de conocimiento general que la mayoría de los pacientes acuden de primera instancia a los médicos primarios cuando padecen de un síntoma o una enfermedad. Usualmente, el médico primario se expone a las diferentes etapas en que puede presentarse una enfermedad; ej., etapa de latencia (asintomática), etapa sintomática, etapa final, o resultados de la enfermedad. Considerando lo expuesto anteriormente, podemos concluir que la medicina primaria provee un taller clínico vasto para la investigación clínica.

Reconociendo las oportunidades que tiene el médico primario para desarrollar la investigación, es necesario identificar cuidadosamente el tema de investigación de interés. En la Tabla I se exponen las diferentes áreas de investigación primaria.² Una vez elegida el área para investigarse, procedemos, en primer lugar, a formular la pregunta del estudio ("research question"). Esta debe formularse de una forma clara y precisa. En segundo lugar se ha de hacer una revisión esmerada de la literatura existente que es relevante al tema a investigarse. Luego se elabora un protocolo de investigación el cual debe ser específico.³ De ser necesario, se deben buscar consultores apropiados tempranamente para discutir los métodos investigativos y estadísticos a utilizarse. Deben existir facilidades adecuadas para la colección y análisis de los datos. Los asuntos éticos relevantes deben ser tratados luego de que todos los arreglos de colaboración estén asegurados. Todo el tiempo se requiere un compromiso sustancial del investigador para mantener y concluir el proyecto.

Tabla I

Áreas de Investigación en la Medicina Primaria

A. Servicios de Salud

1. Oferta y demanda de servicios médicos
2. Patrones de consulta en una comunidad
3. Eficiencia y patrones de utilización de los proveedores
4. Distribución de los proveedores
5. Modelos de medicina primaria

B. Educación

1. Costos de los programas de residencias
2. Métodos de autoevaluación
3. Necesidad de Educación Médica Continuada

C. Epidemiológicos

1. Efectividad de la Medicina Preventiva
2. Estudios de morbilidad
3. Salud ambiental
4. Estudios de incidencia y prevalencia

D. Medicina Clínica

1. Problemas geriátricos
2. Análisis de decisiones clínicas
3. Medicina ocupacional
4. Diagnóstico precoz
5. Efectividad de tratamiento

E. Conducta

1. Impacto de los cambios sociales en la medicina
2. Prevención de crisis
3. Dinámica familiar
4. Relación médico-paciente

Métodos Básicos de Investigación

Una vez que se haya identificado la variable a estudiarse, se procede a considerar los diferentes métodos investigativos que pueden utilizarse para el estudio de esta. En general, los métodos de estudios investigativos se clasifican en dos áreas: los estudios observacionales y los estudios experimentales. Los estudios observacionales generalmente son aquellos en los cuales no se hace una intervención deliberada por parte del investigador. Los eventos ocurren de forma natural y los cambios observados son documentados según ocurren. Los estudios experimentales son aquellos en los cuales el investigador planifica una intervención o manipulación de las variables para ver cual es el efecto del cambio en la variable de interés. A través del control cuidadoso de la situación experimental se puede estudiar la relación de causa y efecto entre las variables de estudio. Ambos diseños tienen sus ventajas y desventajas; estas deben ser pareadas con la variable a investigarse.

Estudios Observacionales

Los estudios observacionales pueden ser clasificados en dos tipos: descriptivos y analíticos. El propósito de los estudios descriptivos es describir cuidadosamente la forma en que ocurren y se relacionan las variables específicas de la pregunta del estudio. Se basan usualmente en las características de una enfermedad en una población dada. Su enfoque está dirigido a la prevalencia e incidencia de un evento y la relación de este con las características básicas del grupo estudiado.^{4, 5}

Los estudios analíticos se llevan a cabo con el propósito de identificar la asociación entre variables. Es de todos conocido que los estudios observacionales están sujetos a numerosas fallas y sesgos potenciales. Por lo tanto, van a requerir pericia en el diseño y cautela en la interpretación. Usualmente las preguntas investigadas en los estudios analíticos se basan en los resultados de estudios descriptivos previos.^{4, 5}

Estudios de Prevalencia (Cross-Sectional Studies)

Los estudios de prevalencia se utilizan para examinar la relación entre enfermedades existentes y características (variables) de una población definida. Cada miembro de la población definida o una muestra representativa de esta, son estudiados para determinar la presencia de una condición y la ausencia o presencia de las variables de estudios. Luego de que los datos son coleccionados, la población se divide en grupos. Las variables estudiadas y la prevalencia de la enfermedad son comparadas a través de los distintos grupos. Los datos también pueden ser utilizados para desarrollar la categoría de la enfermedad. Luego se estudia la relación de las variables con cada categoría. Ambos enfoques permiten examinar la relación entre una enfermedad específica y las variables seleccionadas según su existencia en un tiempo dado en una población definida.^{4, 5}

Estudios de Caso-Control ("Case Control Studies")

Los estudios de caso-control ("case-control studies") consisten en la comparación de un grupo de individuos

que padecen una enfermedad (los casos) con un grupo de individuos en los cuales dicha enfermedad está ausente (grupo control). Los casos y los controles son comparados con relación a atributos existentes o eventos pasados que pueden ser relevantes al desarrollo de una enfermedad o condición que se esté investigando. Generalmente, las comparaciones de casos y controles se llevan a cabo en términos de proporción de casos versus la proporción de controles que exhiban una característica en particular. Si se demuestra que una variable se relaciona desproporcionalmente con los casos en contraste con los controles, entonces existe una asociación observable. Los estudios de caso-control se utilizan para el estudio de enfermedades menos frecuentes. Este tipo de estudio no puede establecer la incidencia o prevalencia de una enfermedad. La confiabilidad de este tipo de estudio va a depender de la habilidad para seleccionar el grupo control.⁶

Estudios de Incidencia ("Cohort Studies" "Longitudinal Studies")

En un estudio de cohorte, un grupo de individuos es seleccionado para ser observado a través de un período de tiempo. El grupo es seleccionado porque no padece la enfermedad o condición de interés. Las medidas están dirigidas hacia proveer información específica sobre la etiología de una enfermedad. Para analizar los datos, el grupo se divide en subgrupos de acuerdo con la presencia o ausencia de alguna característica presente o ausente al comienzo del estudio. Se hacen comparaciones de la incidencia subsiguiente de la enfermedad en los subgrupos. Debido a que la incidencia comparativa es calculada a lo largo del período de tiempo que el grupo es observado, los estudios de cohorte toman mucho tiempo en completarse. Generalmente, estos no son utilizados para estudiar enfermedades de baja incidencia.^{4, 5}

Estudio Experimental ("Experimental Studies")

Según expresado anteriormente, la característica que distingue los estudios experimentales es la manipulación o intervención dirigida del investigador. En la medicina el ejemplo clásico de estos tipos de estudios son los Estudios clínicos experimentales ("clinical trials") los cuales se han establecido como la forma más confiable de evaluar medidas terapéuticas alternas y aplicación de tratamientos apropiados.^{5, 7}

En los últimos 30 años los estudios clínicos experimentales aleatorios ("random clinical trials") se han convertido en el método por excelencia en la práctica médica donde se aplica el método científico. En un experimento clínico se interviene con un grupo experimental. Los resultados de esta intervención son comparados con los de un grupo control que no recibió la intervención. Los resultados obtenidos se presume que sean el efecto de la intervención, estipulando que estos mismos resultados no se observen en el grupo control. Los estudios experimentales provee la mejor evidencia para medir una relación de causa y efecto.^{5, 7}

Hay varias maneras de llevar a cabo estudios experimentales en el ambiente clínico. Las comparaciones de grupo pueden ser hechas con otros grupos que han tenido

intervenciones distintas. Se dice que un experimento es ciego ("blind") si los sujetos de estudio no están concientes del grupo el cual han sido asignados: si al grupo control o al grupo experimental. El término estudio doble ciego ("double blind study") se refiere a un experimento clínico donde tanto los sujetos como el evaluador de los resultados no tienen conocimiento de cuáles de los sujetos del estudio pertenecen al grupo experimental y cuáles pertenecen al grupo control.

El método preferido para la asignación de grupos es el método aleatorio, ya que el azar es la única determinante en la asignación del grupo. La asignación aleatoria permite una mejor aplicación de la técnica estadística. Esta nos ayuda a determinar cuan estadísticamente significativas son las diferencias encontradas entre los grupos al evaluar los resultados. Cuando la asignación aleatoria no es posible, entonces se utilizan métodos quasi-experimentales. En este diseño, por ejemplo, un grupo puede servir como su propio control. Luego de un período de observación establecido, este grupo recibe una intervención dirigida por parte del investigador. La selección del diseño experimental depende de un número de factores como son los recursos disponibles, las consideraciones éticas, las variables a estudiarse, y los instrumentos de medición a utilizarse.^{5, 7}

Conclusiones

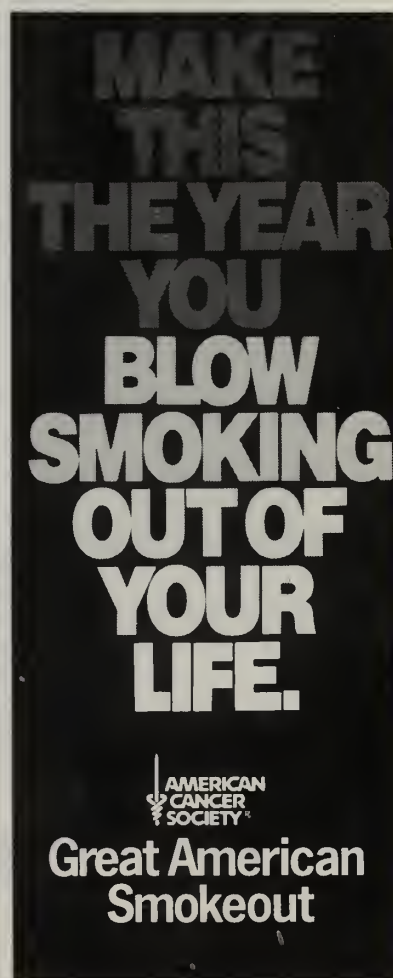
Debido al espectro variado de problemas comunes que se le presentan al médico en la práctica diaria, un conocimiento básico de la investigación clínica le asistiría para ejercer una medicina más efectiva y eficiente. Esta perspectiva clínica estimula al médico mantener una documentación adecuada, la cual es necesaria para establecer la base de datos aceptable para estudios futuros.

El entendimiento del médico primario de los varios métodos investigativos existentes contribuirá a que este evalúe críticamente la literatura médica reportada de tal manera que pueda determinar la relevancia de los hallazgos informados a su práctica clínica. De hecho, una revisión crítica de la literatura médica usualmente es el agente catalizador para que un médico primario se estimule a conducir estudios de investigación clínica que demuestren cuán importante es la perspectiva del mundo de la medicina primaria.

Abstract: Clinical research is analyzed in terms of the primary care setting. Since the primary care physician is the gate keeper in our health care system, he will be exposed to the different stages in which a disease can be present. Due to this fact, he will be able to select a more relevant sample of a population with a given illness. In this article, basic research strategies are reviewed. The understanding of these research methodologies will give the physician the necessary tools to engage in clinical research and critically evaluate medical literature.

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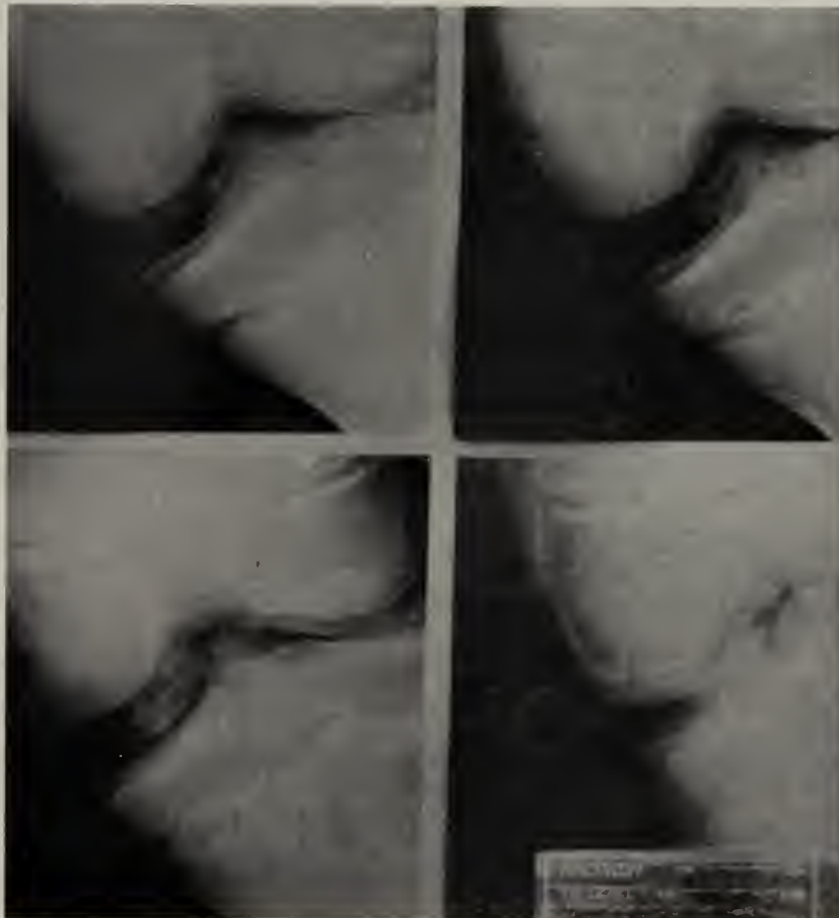
X-Ray Diagnosis

José Anzalotta, MD*

A 12 years old male comes to emergency room of the San Pablo Medical Center complaining pain over the medial aspect of the right knee joint after injury while playing ball. He also states that he has experienced swelling and locking of the knee joint which he is unable to fully extend.

The physical examination shows swelling of the right knee joint with pain to palpation at the medial aspect of the joint, posterior to the medial collateral ligament.

Plain X Ray examination of the right knee shows no evidence of fracture or dislocation. The patient was referred to the orthopedic surgeon who requested a double contrast knee arthrogram. The results are shown in figure 1.



WHAT IS YOUR DIAGNOSIS?

*Director Department of Radiology, San Pablo Medical Center, Bayamón, Puerto Rico.

Diagnosis: Vertical Concentric Tear of the Medial Meniscus

When the fragments of a vertical concentric tear are widely separated it is called a bucket handle tear. (Figure 2) The inner meniscal fragment may be displaced in the intercondylar notch and it is very difficult to see in the arthrogram. The diagnosis is made by the residual deformity in the peripheral meniscal fragment that is short, square off and irregular. When the fragments of a vertical concentric tear are slightly separated, the tear is outlined by contrast and air between the fragments.

A torn meniscus produces locking of the joint when a fragment of the meniscus is caught between the condyles and tibial plateau. The lesion causing locking is frequently the so called bucket handle tear but a tongue-shaped fragment or loose body caught in the joint can produce the same symptoms.

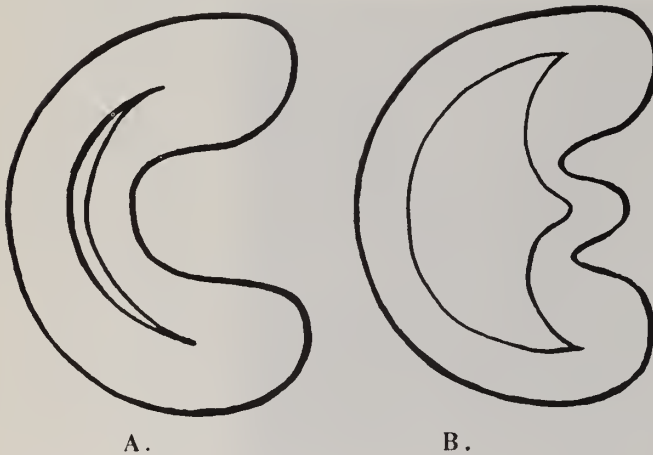


Figure 2
A- Vertical concentric tear
B- Separated fragments of vertical concentric tear called bucket-handle tear.

The meniscus, together with the ligaments of the joint, form a single functional unit. They distribute the weight of the body over a larger tibial surface and serve as a cushion between the femur and the tibial plateau. Thus, removal of the meniscus causes increased pressure per square cm. of the tibial surface at the knee joint in the region of the tibial plateau.

The meniscus enhances the stability of the joint by deepening the joint surfaces and making them congruent. The meniscus prevents the capsule and synovial membranes from invaginating into the joint capsule during knee movements; they are of functional importance for maximum rotation and flexion of the knee joint.

Double contrast arthrography of the knee is a safe and simple procedure which causes only slight discomfort to the patient. The procedure is useful in the evaluation of the internal structures that can not be seen on a plain film. Meniscal tear, degenerative disease of the articular cartilage, loose bodies and popliteal cysts can be readily diagnosed. To obtain a good diagnostic quality arthrogram it is essential to use an X Ray fluoroscopic tube with

focal spot of 0.6 mm or less. Arthrograms performed with X Ray tubes of a focal spot of 1.0 mm or greater have no diagnostic value, as thin meniscal tears can not be diagnosed due to blurring and poor resolution.

The second condition for a good arthrogram is fluoroscopic control to position the knee correctly for proper alignment of the meniscus. Also under fluoroscopy proper exposure can be made to recognize the difference between contrast within the meniscus which indicates a tear and contrast at the menisco-capsular recesses projected through the meniscus. Such distinction eliminates the possibility of diagnosing a false meniscal tear.

The third condition for a good quality double contrast arthrogram of the knee is valgus and varus stress during the filming of the fluoroscopic spot films. This causes widening of the joint compartment under study so that positive contrast and air can cover the surface of the meniscus and outline the meniscal tear easily.

Double contrast arthrography is about 90 percent accurate in the diagnosis of meniscal tear. In the past few years arthroscopy of the knee joint has proven to be a very good technique for the diagnosis of meniscal tear. Arthroscopy shows an accuracy of 90 to 98 percent in the diagnosis of meniscal tear and arthroscopy of the lateral meniscus is more accurate than that of the posterior horn of the medial meniscus.

More recently, magnetic resonance imaging (M.R.I.) of the knee has emerged as the most sensitive diagnostic technique for the detection of meniscal tears.

Suggested Reading

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STUDY: DATA "STRONGLY SUPPORTIVE" OF ALCOHOL-BREAST CANCER ASSOCIATION

An analysis of more than one dozen studies is "strongly supportive" of an association between moderate alcohol consumption and increased breast cancer risk, a report in JAMA finds.

This "meta-analysis," pooling the results of 16 reports published since 1982 on a possible drinking-breast cancer link, also finds "compelling" evidence supporting a dose-response relationship between alcohol and breast cancer risk—that is, the more alcohol consumed, the greater the odds of malignancy.

However, the report's authors, Matthew P. Longnecker, MD, of the Harvard School of Public Health, Boston, and colleagues, caution that they do not interpret their findings as necessarily being proof of a cause-and-effect relationship between drinking and breast cancer. In addition, they note, their study should be viewed in the broader context of data suggesting that moderate drinking may have a protective effect against cardiovascular disease and may be associated with a decrease in total mortality and a reduced risk of hospitalization. "One's particular profile of breast cancer and cardiovascular risk factors might influence personal decisions regarding alcohol use," they say.

Epidemiologic findings about the relationship between drinking and breast cancer "have been inconsistent," the authors say. Therefore, they searched the medical literature for reports on this topic, combined the epidemiologic data found in 16 published papers, letters, manuscripts and abstracts, and used the data to calculate pooled estimates of the effect of drinking on breast cancer risk.

The data came from two kinds of research—case-control studies, which look at patients with the disease or disorder in question and a comparable control population, and follow-up studies, which follow over time a group of subjects who may or may not have the disease or disorder being studied. Case-control studies usually involve a certain point in time and are smaller than

follow-up studies.

This analysis, the investigators report, indicated "strong evidence" supporting a dose-response relationship between alcohol consumption and breast cancer risk, ranging from a weak direct association at light and moderate alcohol intake (approximately one-half to one drink daily) to a modest association at heavier levels of alcohol intake (approximately two or more drinks daily). "Association does not prove cause and effect," the authors write. "The presence of a dose-response relationship supports causality; however, causality is difficult to establish when the effect is modest. There may be some factor that results in both a tendency to drink alcohol and a tendency to develop breast cancer."

An intake levels of 24g (1 oz.) of alcohol daily (about two drinks), drinkers had on the average a 40 percent greater relative risk of breast cancer than non-drinkers in the case-control data studied, and a 70 percent higher relative risk in the follow-up data, the authors estimate. They say they consider the follow-up data "less likely to be biased."

The authors acknowledge the possibility of problems with the meta-analysis technique. However, they note, "the results of meta-analyses of experimental epidemiologic data have been shown to approximate those of the 'gold standard' of large, well-conducted studies."

"In summary, the results of this meta-analysis are strongly supportive of an association between alcohol consumption and risk of breast cancer," the report concludes. "The increased risk that is apparent from these data should not, however, be considered separately from the protective effect of alcohol against cardiovascular disease that is suggested by other studies. With each new piece of evidence, our understanding of this subtle—possibly causal—association will continue to evolve."

JAMA August 5, 1988

NOT ENOUGH DATA TO GENERALLY RECOMMEND FISH OIL SUPPLEMENTS: REPORT

There is currently insufficient evidence to recommend fish oil supplements for use by the general public, although the low doses suggested in many commercial preparations probably won't harm normal healthy individuals, a report in JAMA concludes.

Some patients with high blood lipid levels might benefit from the medically supervised use of such supplements, writes Jack Zeev Yetiv, MD, PhD, of the Sequoia Hospital, Redwood City, Calif. But, he says, there is not enough data for such a recommendation in other medical disorders, and fish oil supplements need to be avoided in some cases because of potentially serious side effects.

"These include occasional adverse lipid changes, potential for bleeding and vitamin E deficiency, and, with

some preparations, vitamin A and D toxicity," Yetiv writes in an extensive review of reports in the medical literature on the potential benefits of fish oils. While a general recommendation of supplements is premature, an increase in fish intake "seems reasonable," he concludes.

Much of the current interest in fish oils, or their active ingredient, Omega 3 fatty acids, stems from observations that Eskimos rarely die of cardiovascular disease, possibly because their diets, while high in fat and cholesterol, contain large amounts of seafood. Several other epidemiologic studies also have suggested the beneficial cardiovascular (and possibly other) effects of eating fish, but "not all studies have shown such a relationship," Yetiv says.

Fish and fish oil supplements are believed to lower plasma lipid levels (especially triglycerides), inhibit platelet aggregation, and may decrease blood pressure and viscosity and increase high-density lipoprotein (HDL) levels, Yetiv's review indicates. "Preliminary observations also suggest a *potential* future role for fish oils in the treatment of some autoimmune diseases, such as atopic dermatitis, psoriasis, and rheumatoid arthritis," Yetiv writes, but he does not recommend such treatment at present.

"Most researchers recommend increasing the intake of seafood rather than taking supplements," he writes. "It seems reasonable to increase fish intake at least to the levels noted to be beneficial in (one) epidemiological study—two or three fish dishes a week"—ideally, replacing meat or other high-saturated fat foods.

Children, adolescents, pregnant women, patients on anticoagulants, or those with known or suspected bleeding disorders should *not* take fish oil supplements, Yetiv says. "Little is known about fish oil use in the first three groups of patients and, of relevance to pregnancy, high doses of fish liver oils may, secondary to vitamin A content, (cause birth defects). The last two groups are usually in a precarious antithrombotic balance, and addition of substances that increase bleeding tendency may lead to serious, or perhaps even fatal, bleeding."

Patients being treated for a serious medical disorder should discuss any plans to take fish oil supplements with their physician, Yetiv says. Doctors choosing to prescribe the supplements "should be vigilant for side effects and drug-drug interactions that may be as yet unknown," Yetiv says.

Patients with high serum triglyceride or cholesterol levels "may reasonably be treated with fish oils under medical supervision," he writes. But, "as is true of other hypolipidemic agents, fish oil supplementation should only be attempted after a serious attempt at dietary therapy has proved inadequate." Despite limited clinical experience, Yetiv says, "I believe that data currently available demonstrate sufficiently high efficacy with low risk of side effects to justify a trial of fish oil supplementation."

That having been said, however, Yetiv says he cannot recommend supplements for normal healthy individuals. Although similar to the amount of fish oil ingested in some epidemiologic studies, the clinical value of daily dosages generally recommended by supplement manu-

facturers "is speculative, since no long-term interventional studies of low-dose fish oil intake have been published. It is unlikely, however, that such a low dose of (Omega 3 fatty acids) would have any significant deleterious effects."

JAMA August 5, 1988

CASE FOR HEART DISEASE-PREVENTING DRUG STRENGTHENED: STUDY

A study in JAMA offers further evidence that the drug gemfibrozil reduces the incidence of coronary heart disease in hypercholesterolemic men by lowering their levels of lower-density lipoprotein (LDL) and by raising their levels of high-density lipoprotein (HDL). The study analyzed data from the Helsinki Heart Study, a randomized, double-blind trial, which followed for five years 4,081 middle-aged men, who had abnormally high serum cholesterol levels but no symptoms, say the authors, Vesa Manninen, MD, of the University of Helsinki, Finland, and colleagues. The authors say the incidence of coronary heart disease (CHD) was 34 percent lower among men receiving gemfibrozil than those on placebo. Averaged over five years and compared with the placebo group, the drug group had a 10 percent mean decrease in total serum cholesterol, an 11 percent mean decrease in LDL levels, and a mean increase of 11 percent in HDL from baseline levels measured before treatment. The researchers found even stronger positive effects among subjects who were more compliant with the drug regimen. "Thus, the results of this study, together with earlier observations, suggest that both elevating HDL cholesterol levels and lowering LDL cholesterol levels are effective in the primary prevention of CHD," the authors conclude.

JAMA August 5, 1988

MORE EVIDENCE THAT ASPIRIN CAN CAUSE REYE'S SYNDROME

The incidence of Reye's syndrome increases with doses of aspirin given children to treat chickenpox or other viral illness, says a study in JAMA. Reye's syndrome is a serious, often fatal illness that affects some children following a viral infection. Aspirin is strongly suspected as having a causative role since studies have shown that most cases occur among children who have taken the drug, say the authors, Paul F. Pinsky, MPH, and colleagues at the Centers for Disease Control, Atlanta. The authors found a strong dose-response effect in data collected by the Public Health Service Main Study of Reye's Syndrome and Measles. Among those given aspirin for their viral illness, patients who later developed the syndrome "were four times more likely to have received greater

average daily and maximum daily doses of aspirin and greater doses of aspirin on the first four days of the antecedent illness (median, 25.1 mg/kg; 33.0 mg/kg; and 65.4 mg/kg; respectively) than did controls (median, 14.5 mg/kg; 19.0 mg/kg; and 27.0 mg/kg; respectively)," they report. "In addition to providing supportive epidemiologic evidence for the causal association between Reye's syndrome and aspirin, these analyses may provide further clues to the pathophysiology of this illness." The authors conclude that "it must be assumed that no safe dose of aspirin exists and that avoidance of this compound for treating children and teenagers with chickenpox or respiratory illness is the most effective means of reducing the risk of developing this illness."

JAMA August 5, 1988

EFFECTS OF RADIATION EXPOSURE ON SENSE OF SMELL

The sense of smell can be seriously impaired by radiation used to treat head and neck cancer, concludes a study in the August *Archives of Otolaryngology-Head and Neck Surgery*. In their study, Dov Ophir, MD, of the Kaplan Hospital, Rehovot, Israel, and colleagues tested olfactory acuity in 12 patients whose olfactory mucosa were exposed to radiation during treatment for nasopharyngeal carcinoma or pituitary adenoma. Tests showed the patient's sense of smell was "profoundly affected" by the radiation, the authors say. Varying of recovery were seen in most patients three to six months after treatment, but "none...showed full recovery even six months after cessation of treatment," the authors find. "The fate of the sense of smell deserves more attention when considering the disability caused by irradiation to certain head and neck tumors," they say.

REMOVING PERMANENT EYELINER

Permanent eyeliner, pigment tattooed into the eyelids along the eyelash border, can be removed, but a letter in August's *Archives of Ophthalmology* suggests it is not a process to be undertaken lightly. Recommended techniques for removing permanent eyeliner include surgical excision, bleaching the pigment by applying alcohol with a tattoo needle, applying a lighter pigment over the existing eyeliner, and scraping off the pigment with a curette, write Chicago ophthalmologists Allen M. Putterman, MD, and Michael E. Migliori, MD. They describe performing the delicate elective excision technique on a 40-year-old woman who was unhappy with the appearance of her lower eyelids after undergoing the eyeliner procedure. "Both thorough knowledge of eyelid anatomy and careful dissection are necessary to excise the pigment, preserve eyelid structures, and minimize scarring (which can cause the eyelid to turn inward or outward)," they say. They report a successful outcome in this patient, who was pleased with the result even though some residual pigment remained along the lower lash borders.

MOVING MEDICAL ETHICS FROM CLASSROOMS TO PATIENTS' BEDSIDES

The field of medical ethics is moving from the classroom to the patient's bedside, changing the way medical decisions are being made in hospitals, clinics, and doctors' offices, say reports in JAMA.

A related editorial by Edmund D. Pellegrino, MD, of Georgetown University, Washington, DC, says the intuitive and idiosyncratic way ethical choices have been made in medicine in the past is no longer tenable. "Medical ethics has become a public affair," Pellegrino writes. "The physician's decisions must now be justified to patients and their families, one's colleagues, and the courts."

The three accompanying reports describe the experience of the ethics committee of the Massachusetts General Hospital (MGH), Boston; the experiences of a newly established formal consultation service at a teaching hospital in Chicago; and the clinical ethical problems encountered in a university-affiliated office practice in internal medicine. Taken together, these studies "provide a picture of what clinical ethics is, who practices it, what research it fosters, and what new questions must be faced as the field gains maturity," Pellegrino writes.

In the first study, Troyen A. Brennan, MD, JD, MPH, of Brigham and Women's Hospital and Harvard Law School, Boston, examines the MGH committee's usefulness in helping physicians decide whether to limit care for terminally ill patients. While medical technology has done much to improve the care of the critically ill, for many patients and their families, the suffering and sorrow that surround death are often greatly exacerbated by medical intervention, he says.

The committee—composed of a nurse, a surgeon, an internist who is also a lawyer, and the chairperson, a psychiatrist with a divinity degree—is generally consulted when an ethical problem involves especially sensitive issues or when there is a disagreement between treating physicians. The panel's role is strictly advisory and bases its decision mainly on what would be the best thing to do for the patient. The committee "often reassures caregivers that withdrawal of care is ethically defensible once it is clear that the disease process is irreversible and the patient moribund," Brennan say.

The committee had to confront unsettled ethical and legal questions in cases where physicians disagreed with families' wishes for continued invasive care for an incompetent, terminally ill patient, when those wishes were clearly unrealistic or irrational. While the argument that physicians should not usurp the family's decision-making role is powerful, doctors may resist being forced against their ethical judgment to provide useless treatment, the committee advised: "The patient's dignity and integrity outweighed whatever psychological benefit the family would gain from knowing that further invasive, yet useless, procedures would be pursued," Brennan writes.

Though rational and consistent with ethical principles,

the committee's approach must be considered controversial, he says. Although the law is unclear, in all cases where the committee's advice was followed, families either ultimately accepted its reasoning or stopped insisting on invasive procedures, with no lawsuits resulting. The committee's experience provides a valuable model, Brennan concludes. During the 13 years of consultation studies, it "dealt with controversial issues in a consistent and ethically forthright manner..."

A growing number of hospitals are beginning to rely on ethics consulting services instead of ethics committees. Unlike committees, which are "unwieldy and may lack the clinical expertise to help individual clinicians," a formal consultation service may provide advice that is more readily accepted by physicians, say John La Puma, MD, and colleagues at the University of Chicago Hospitals and Clinics, who describe one such service in a second *JAMA* article. Assistance with decisions to forego life-sustaining treatment was the most common reason for consulting a newly established ethical consulting service at their institution, they report. In 71 percent of cases studied, the requesting physicians stated that the consultation was "very important" for patient management, in clarifying ethical issues, or in learning about medical ethics. In 96 percent of cases, the physicians indicated they would request ethics consultation in future.

In the third report, Julia E. Connelly, MD, and Steven DalleMura, MDiv, of the University of Virginia, Charlottesville, examine the ethical problems encountered in medical offices, where ethical dilemmas are usually seen as less dramatic than those encountered in hospital settings, and where decisions made are seldom as momentous. Nevertheless, the ethical problems arising in office practice may jeopardize the care of patients and disrupt the relationship between patients and physicians, the authors write.

Their study examined the ethical problems presented by patients in a university-affiliated general internal medicine office practice. Nearly one-third of these patients presented ethical problems that influenced their health care. These problems include questions of patient competence and capacity to choose treatment, refusal of treatment, confidentiality, and family conflicts affecting treatment. While these problems were common in all age groups, they were more prevalent in patients over age 60, the authors report.

In his editorial, Pellegrino, who heads the Kennedy Institute of Ethics at Georgetown, looks at who and what qualifies a consultant as an ethics expert. The accompanying reports provide "evidence of cooperation between physician-ethicists and nonphysician ethicists," he writes. "In many medical schools, nonphysician ethicists have demonstrated an impressive grasp of clinical details and have been accepted as consultants and teachers of faculty and students. Some have even acquired the badges of the white coat and the beeper."

There is no reason, he says, why nonphysicians cannot learn enough about the clinical facts to make ethical judgments, nor why physicians cannot learn enough about ethical analysis to use it in their own cases or others. "Let us hope then that the resolution of the question of who

shall consult is decided more by the capacity to function effectively than by professional identification."

JAMA August 12, 1988

MATERNAL BRAIN DEATH DURING PREGNANCY

A report in *JAMA* describes the case of a healthy infant born to a 27-year-old pregnant woman maintained in a brain-dead state for nine weeks so her fetus could mature. This is thought to be only the second reported case in which prolonged "somatic support" of the mother resulted in the birth of a surviving baby and represents "the longest period such maternal support has been maintained," David R. Field, MD, now with the Naval Hospital, Oakland, Calif., and colleagues write. The infant weighed 1,440 grams (3.2 pounds) when delivered via cesarean section at 31 week's gestation and did well. Despite the demanding technical aspects in this case and the high cost —\$217,784— there are ample ethical arguments justifying the separation of brain death and somatic death and the maintenance of the brain-dead mother so that her unborn fetus can develop and mature," the authors say. But, they add, this does not mean such measures should be taken in all such cases. "Rather than proposing strict guidelines, we believe that when these rare cases appear, the decision of whether to proceed with prolonged cardiorespiratory support should be based on the particulars of each case," they conclude.

JAMA August 12, 1988

PROTECTIVE EFFECT FROM LONG-WAVE ULTRAVIOLET RADIATION?

Many studies link exposure to broad-spectrum ultraviolet (UV) radiation with skin cancer; medium-wave ultraviolet radiation, (UV-B), is known to be sunlight's most carcinogenic component. But a Scandinavian study in the August *Archives of Dermatology* says hairless mice experimentally exposed to long-wave ultraviolet radiation, (UV-A) —similar to wavelengths emitted by most tanning salon units— were significantly protected from developing tumors when later exposed to UV. The authors, Niels Bech-Thomsen, MD, of the Rigshospital, Copenhagen, Denmark, and colleagues, say pre-irradiation of the mice with UV-A inhibited development of UV-induced skin tumors in two independent experiments. They also say UV-A exposure caused no visible skin changes, nor changes in skin thickness or melanin content. The authors say their results raise some interesting issues but note that numerous questions must be answered "before it is possible to devise a more general model concerning the protective effects of pretreatment with UV-A." Even

greater caution is urged in a related editorial in August 5's *Journal of the American Medical Association*. Robert S. Stern, MD, of Beth Israel Hospital, Boston, calls the study "provocative" but says the protective effect of UV-A reported in the experiment "is unlikely to apply to the human exposure situation." "Unlike the study... in which the mice had never been exposed to UV-B or sunlight before exposure to UV-A, the sequence of human exposure includes UV-B before UV-A and vice versa," he writes. "For humans, it is most likely that no matter how acquired, an equal tan results in equal damage to the skin."

STUDY: CHRONIC FATIGUE LINKED TO PSYCHOLOGICAL, NOT PHYSICAL FACTORS

Chronic fatigue is a widely reported ailment but appears associated more with depression and anxiety than with specific physical disease, a study in *JAMA* suggests.

Nearly one in four patients visiting two primary care clinics in San Antonio, Texas, considered chronic fatigue a "major problem," reports the study by Kurt Kroenke, MD, of the Brooke Army Medical Center, Fort Sam Houston, Texas, and colleagues. Diagnostic tests showed no physical medical problem more prevalent among fatigued patients than among a control group, but psychological tests suggested that fatigued patients were much more likely to suffer depression and/or somatic anxiety (physical symptoms of anxiety) than the controls.

Of the 1,159 patients surveyed, 276 (24 percent) indicated fatigue was a major problem, the study says. Extensive clinical, laboratory, psychometric, and functional data then were gathered for 102 fatigued patients and 26 controls. "Laboratory testing was not useful in detecting unsuspected medical conditions or in determining the cause of fatigue," the authors say. "In contrast to laboratory testing, psychometric and functional profiles showed clear distinctions between groups." Fifty-six percent of the fatigued patients had scores suggestive of depression, versus none of the controls; 57 percent of the fatigued patients had scores suggesting somatic anxiety, versus 12 percent of the controls. Considered together, 80 percent of the chronically fatigued patients had abnormally high scores for depression or somatic anxiety, compared with 12 percent of controls.

The authors urge caution in interpreting their data, noting that "abnormal scores are neither specific for psychological disease nor can they accurately place patients into diagnostic categories." The associations also do not prove cause and effect—fatigue and depression may stem from "an unrecognized physical illness," the researchers emphasize.

But they say the powerful and consistent results of their psychometric tests, combined with an absence of physical and lab differences between the two groups, strongly suggest emotional factors play an important role in chronic fatigue.

The authors found the degree of dysfunction reported by chronically fatigued patients similar to those reported by patients with untreated hyperthyroidism and in survivors of cardiopulmonary resuscitation. "Physicians may underestimate their patients' functional limitations, resulting in inadequate treatment and patient dissatisfaction," they conclude. "the high prevalence, persistence, and functional consequences of fatigue mandate a search for effective therapy."

A related study in *JAMA* reports that testing for antibodies to the Epstein-Barr virus (EBV)—the virus that causes infectious mononucleosis—serves no purpose in evaluating patients who suffer chronic fatigue and should no longer be done. Although earlier reports have suggested chronic fatigue syndrome may be caused by a chronic or reactivated EBV infection, more recent studies have raised doubts about this association, say the authors, Walter C. Hellinger, MD, of the Mayo Clinic, Rochester, Minn., and colleagues.

Although their study did not examine whether chronic fatigue may be caused by lingering mononucleosis, it did examine whether the presence of EBV antibodies was associated with any clinical problem in the chronically fatigued. The authors compared 30 chronically fatigued patients, who had highly elevated serum levels of an antibody to EBV, with 30 control patients, who suffered fatigue but had none of the antibodies. The patient's medical records were along with their answers to a follow-up questionnaire evaluating the amount of work they missed and number of medical visits made due to fatigue.

The authors report no significant differences between the clinical condition of subjects and controls or between their answers to the questionnaire. "We believe that our study raises serious questions about the usefulness of measuring antibody to (EBV) in the evaluation of patients with indeterminate fatigue," they conclude. "Given the expense of this test and the absence of clinically useful information derived from it, we suggest that its current use in the clinical evaluation of patients with chronic fatigue be abandoned."

JAMA August 19, 1988

TREATING OCULAR MELANOMA THAT HAS SPREAD TO THE LIVER

A new treatment scheme using an anticancer drug/polyvinyl sponge mixture can greatly improve survival for patients with ocular melanoma that has spread to the liver, a disease that "previously was virtually resistant to any conventional chemotherapy," a study in *JAMA* says. Ocular melanoma is diagnosed in some 2,000 Americans yearly, spreading to the liver in many of these, say researchers Giora M. Mavligit, MD, of the University of Texas M.D. Anderson Cancer, Houston, and colleagues. Response to therapy and survival are poor once this occurs. But the authors report improved results with a mixture of the drug cisplatin and polyvinyl sponge

particles, injecting this directly into the hepatic artery. They saw tumor regression of at least 50 percent in nearly half of 30 patients treated; one had complete regression. Median survival for the group was 11 months, compared with two to six months with conventional therapy. The cisplatin/sponge mixture seems to work by increasing tissue retention of the anticancer drug, the authors say.

JAMA August 19, 1988

PENILE IMPLANTS ASSESSED

Four currently used inflatable or semi-rigid penile implants are safe and effective means of treating impotence that won't respond to medical management, an AMA science review panel concludes in a report in JAMA. The 21-member Diagnostic and Therapeutic Technology Assessment (DATTA) panel reviewed one inflatable and three semi-rigid implantable prostheses used in treating impotence. At least 95 percent of the panelists (100 percent in the case of one semi-rigid implant) considered the devices to be established in terms of both safety and effectiveness, even though "each of these prostheses has its own advantages and disadvantages," the report says. "Patients considering this surgery must be thoroughly evaluated for the cause of their impotence prior to surgery," the report notes.

JAMA August 19, 1988

VITAMIN C MEGADOSES

Some marijuana smokers believe that ingesting megadoses of ascorbic acid will "clean" their urine of the cannabis detectable by drug testing, but those who count on this practice "are in for an unwelcome surprise," says a letter in the August *Archives of Pathology and Laboratory Medicine*. Richard H. Schwartz, MD, of Vienna, Va., and Stuart Bogema, PhD, of American Medical Laboratories, Fairfax, Va., write that some pot smokers will ingest large quantities of vitamin C tablets, a homeopathic product called golden seal root, or acidic beverages such as cranberry juice, believing this will change cannabis metabolism or excretion patterns and sanitize "dirty" urine. The authors tested this theory using five volunteers from the National Organization for the Reform of Marijuana Laws. Each smoked at least one marijuana cigarette, after which urine samples were taken. Each then ingested 3,000 mg of ascorbic acid, 1,560 mg of golden seal root, and 750 mL of cranberry juice cocktail, after which more urine samples were taken. Laboratory tests detected cannabinoids in all specimens; these levels were reduced after ingesting the various forms of ascorbic acid, but this likely was due to the diluting effect of the cranberry juice, the authors say.

ANGIOGRAPHY RISK TO MIGRAINE SUFFERERS?

Some studies have suggested that patients suffering from migraine may be at increased risk of developing complications as a result of cerebral angiography, not an uncommon procedure in migraine patients seeking treatment for an unusual headache or other conditions. But a report in the August *Archives of Neurology* concludes that a history of migraine doesn't increase the risk of complications during angiography, which is used to obtain images of cerebral blood vessels. What's more, report authors Ashfaq Shuaib, MD, now with the Foothills Hospital, Calgary, Alberta, Canada, and Vladimir C. Hachinski, MD, of University Hospital, London, Ontario, Canada, angiography during episodes of acute headaches also appears to be a safe procedure, although transient neurological symptoms are not infrequent. The study involved a review of the medical charts of 142 migraine patients who underwent a total of 149 angiograms for a variety of reasons. Complications developed in seven patients; they were temporary in six. The rate of temporary focal cerebral complications in this group (amnesia, partial paralysis) was comparable to that seen in another group of more than 1,000 patients at the same center, the authors say. "A history of migraine should therefore not be considered a contraindication to angiography," they conclude.

U.S. MEDICAL SCHOOL APPLICATIONS, ENROLLMENTS DOWN

Applications to U.S. medical schools declined for the 1987-88 academic year and first-time enrollments fell for the sixth year in a row, according to a report in JAMA.

The number of women enrolling in and graduating from medical schools continues to rise, although the number applying has declined, says JAMA's 88th Annual Report on Medical Education in the United States. The percentage of medical students from minority groups has changed little over the past few years, although the number of minorities enrolled has fluctuated. However, the number of white males entering medical school has declined in the past five years, while the number of black, Asian, and Pacific Islander women has increased substantially, the report says.

There were 3,200 fewer applicants to U.S. medical schools for the 1987-88 academic year than the year before, writes Anne E. Crowley, PhD, of the AMA's Office of Medical Education Information Analysis. Of 28,123 applicants, 17,027 were accepted by at least one school for fall 1987 enrollment.

First-time enrollment totaled 16,047, "a continuation of the decrease observed over the past five years," the

report says. Total enrollment, 65,742, also was down for a sixth straight year. "Despite the decline in number of applicants, the percentage of 'A' students entering has increased and the average Medical College Admission Test score of entering students remains high," The authors say.

Women accounted for 37 percent of 1987-88 medical school applicants (58 percent of those applying were accepted), 36.5 percent of entering classes, 34.3 percent of total enrollment, 32.7 percent of MD graduates and 28 percent of residents in graduate medical education programs. Female residents are found in nearly all specialties, but two-thirds are training in family practice, internal medicine, obstetrics/gynecology, pediatrics, or psychiatry.

In discussing minority enrollment, the report looks at ethnic groups underrepresented in medical school when compared with their representation in the overall U.S. population. These groups account for 10.6 percent of the 1987-88 student body —6.2 percent blacks, 4 percent Hispanics and 0.4 percent native Americans. Ten percent of residents were from underrepresented groups.

Just under 10 percent of students in accredited U.S. medical schools during the 1987-88 year were not U.S. citizens, down sharply from a year earlier. About 16 percent of residents on duty in 1987-88 were foreign medical school graduates.

Ther report also includes financial information for the 1986-87 fiscal year, compiled by the Association of American Medical Collegues. Medical school tuition and fees increased 6 percent from 1985-86, down a bit from a year earlier, but they "remain a small fraction of total revenues" at 5.3 percent.

The report notes that financial aid to medical students in 1986-87 increased 13.8 percent over 1984-85, with 77 percent of assistance in the form of loans. Students graduated in 1987 an average of \$35,621, up from the \$33,500 the year before. Seventeen percent of 1987 graduates had debts topping \$50,000.

The number of students expected to graduate in 1988 was estimated at press time at 15,947, 111 more than a year earlier; 55 percent accepted residency positions in primary care specialties. As of Sept. 1, 1987, there were 81,410 residents on duty in accredited programs in the U.S., 4,595 more than a year earlier, with more than two-fifths in family practice, internal medicine or pediatrics programs.

The report says 66,798 full-time faculty provided instruction for medical students in 1987-88. Faculty members also were responsible for providing some instruction for students in other health professions, conducting continuing education courses for practicing physicians, and for research and patient care.

The report also notes that 40 percent of U.S. medical schools have policies regarding students who test positive for human immunodeficiency virus and/or are diagnosed with AIDS or AIDS-related complex. Another 46 percent of the schools are considering such policies.

JAMA August 26, 1988

EVALUATING THE COMPETENCE OF HEALTH PROFESSIONALS

The evaluation of competence is emerging as the most important and controversial issue affecting the education of health professionals, says an editorial in JAMA.

"The emphasis on competence arises from a growing demand for public accountability in all health professions, from the continuous increase in the cost of medical care, from the tremendous explosion in technology and new knowledge, and particularly from a growing concern about the importance of ethical behavior of health professionals," writes Carlos J.M. Martini, MD, MPH.

Martini, AMA Vice President for Medical Education, says there is a need to redefine what professional competence means and to examine the mechanisms for evaluating competence. Until now, he says, the medical education system has worked well, generating some of the world's most able and successful practitioners and programs. But it is imperative to periodically stop, review, and make appropriate corrections to the system to ensure that minimum standards of quality are preserved, he says.

Evaluations of the medical education system should take into account the "final product" or "outcome" of the education process, Martini writes. This is not done now as much as it should due to the difficulty of defining what is a "competent" medical professional, and due to questions about the validity of traditional evaluation measurements, which consist mainly of sets of examinations and personal observations, he says.

The most valid means of measuring the outcome of education may be by "observing 'what is done' rather than by finding out if the practitioner 'knows how to do it,'" he suggests. Though difficult, evaluating outcome is certainly not impossible; the new clinical simulations of the National Board of Medical examiners and the use of "standardized" patients in some medical schools for assessment purposes are two examples he cites. "The challenge now is to further improve our excellent but still limited evaluation mechanisms and to incorporate valid and reliable measurements of health professionals' competence that consider health practitioner's behavior as well as their knowledge and skills."

Health professionals must lead these efforts, he says. The first priority should be to redefine in evaluative terms what professional competence means, with particular attention to health professional's behavior and the humanistic responsibilities of medical science. Other priorities should include further evaluation of the medical accreditation process to determine the validity of standards used; the assurance that minimum standards are applied universally to all practitioners, independent of the place of training and practice of their specialty and pattern of practice; and involving the public more in the process of defining what is the desirable product of medical education.

JAMA August 26, 1988

ETHICAL QUESTIONS RAISED IN GERMAN BRAIN RESEARCH

Two brain specimens included in a 1985 schizophrenia research article in the *Archives of General Psychiatry* may have resulted from the murders of psychiatric patients in Nazi Germany, letters in August's *Archives* say. This raises a host of ethical issues not only about use of the specimens and the brain collection to which they belong, but about "the bounds of acceptable knowledge from human experiments," write Elliot S. Gershon, MD, and Margaret R. Hoehe, MD, of the National Institute of Mental Health, Rockville, Md. They became concerned about the study after hearing lead author Bernhard Bogerts, MD, of the University of Dusseldorf, West Germany, discuss it at an international meeting. The study involved the brains of 13 schizophrenics and nine control cases belonging to the Vogt collection at the University of Dusseldorf and collected between 1928 and 1953. After hearing from Gershon and Hoehe, Bogerts says he documented that all study subjects died of natural causes except for two 39-year-old schizophrenic twins. "An unnatural cause of death for these two patients cannot be ruled out with certainty. In future studies, therefore, we will not evaluate the brains of these two patients, who died during the darkest chapter in German psychiatry," he writes. The Nazis were known to use twins in studies that were "perversions of clinical genetic research" and murdered large numbers of psychiatric patients, note Gershon and Hoehe, who say Bogerts did not know of the possible source of his data until making further inquiries. They say they wrote their letter not to fix blame, but to sensitive those involved in human research "to the ethical issues raised by the inclusion in a scientific publication of a report on brain specimens of patients who may have been murdered for purposes of research."



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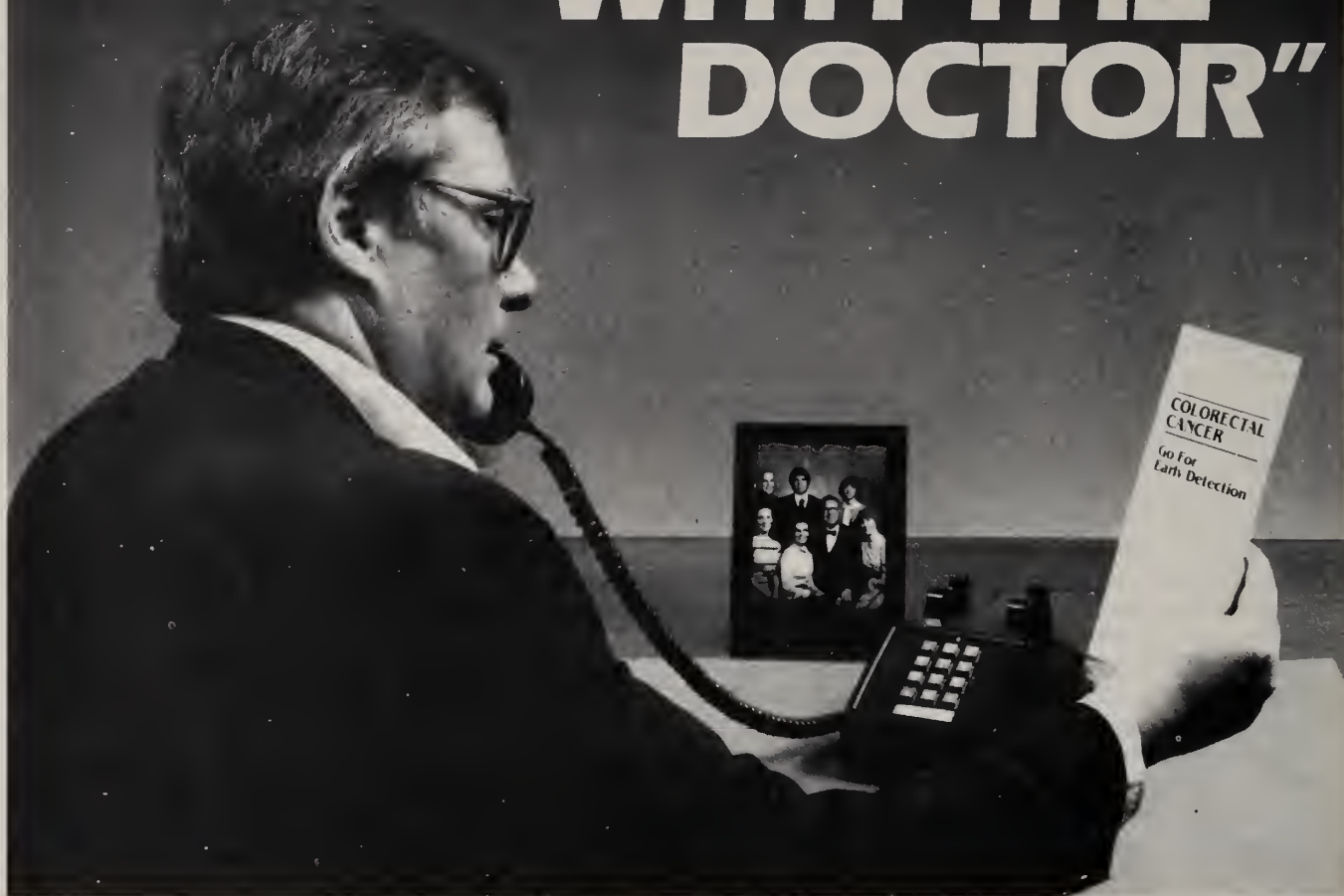


INTRAOCULAR tPA FOR FIBRIN FORMATION AFTER EYE SURGERY

Formation of intraocular fibrin, the insoluble protein that forms the basic part of a blood clot, is a potentially serious complication after vitrectomy, the operation used to treat retinal detachment. But a report in August's *Archives of Ophthalmology* says intraocular use of tissue plasminogen activator (tPA), the new drug used to dissolve blood clots in heart attack patients, appears effective in treating fibrin formation in such patients who don't respond to other therapy. George A. Williams, MD, of the Medical College of Wisconsin, Milwaukee, and colleagues, describe the use of tPA in three such patients who developed severe intraocular fibrin formation within 24 hours of their surgeries. In each patient, the fibrin dissolved within four hours after tPA was injected into the eye. There were no complications, the authors say. "Further experience will better define the risk-benefit ratio of intraocular tPA," they say. "However, in eyes with severe fibrin formation that is unresponsive to conventional treatment, intraocular tPA appears to be an effective therapeutic modality."

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*"Cancer of the Colon and Rectum: Summary of Public Attitude Survey," Ca 33:359-365, 1983 (Nov.-Dec.).

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Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

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Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

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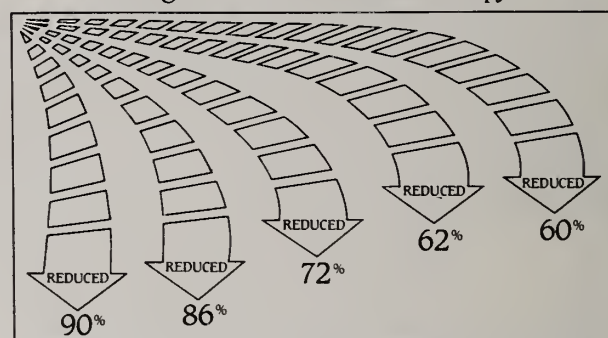
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VOL.80 - NUM. 11

NOVIEMBRE 1988

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Publicación mensual, \$40.00 anuales. El Boletín se distribuye a todos los miembros de la Asociación Médica de Puerto Rico como parte de su cuota anual.

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Boletín de la Asociación Médica de Puerto Rico is published monthly for \$40.00 per year by Asociación Médica de Puerto Rico. 1305 Fernández Juncos Ave. P.O. Box 9387, Santurce, P.R. 00908.

"POSTMASTER" Send address changes to Boletín Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, Santurce, P.R. 00908.

Second Class postage paid at San Juan, P.R.

USPS-060000

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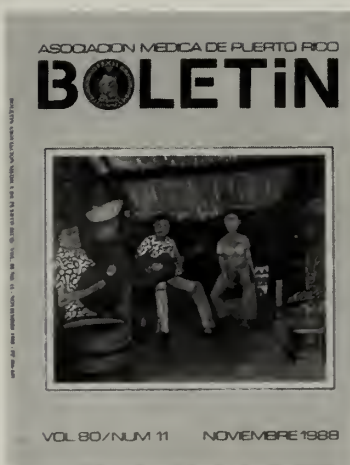
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NUESTRA PORTADA

El Viejo Bolero, óleo sobre tela, 60" x 72", del artista Rafael Ferrer.

El artista nació en Santurce en 1933 de familia acomodada aprendió a tocar percusión en Staunton Military Academy. Se envuelve en la música y dirige una orquesta latina mientras estudiaba en Syracuse University. A la misma vez comienza a dibujar y a pintar y de regreso a la isla ingresa en la Universidad de Puerto Rico donde hace amistad con el pintor español Eugenio Fernández Granell. Granell lo introduce al mundo del Surrealismo y en un viaje a París a través de Granell Ferrer conoce a Andre Breton, Wilfredo Lam, Benjamín Peret, y otras figuras del Surrealismo. En Puerto Rico continúa tocando batería y timbales y forma parte de un grupo de músicos experimentando con ritmos de bomba y plena y ritmos afro-cubanos, entre ellos sus amigos Ismael Rivera y Rafael Cortijo. En el 1954 se muda a Nueva York y persigue su carrera en la música, nunca abandona el arte y en su tiempo libre visita galerías y museos. En 1961 expone en el museo de la Universidad de Puerto Rico y comienza a crear esculturas de acero. Luego de varias exhibiciones locales se muda a Filadelfia en 1966. Comienza a exhibir en las galerías y museos de más prestigio en los Estados Unidos entre ellos —el Whitney Museum of American Art, el Museum of Modern Art de Nueva York y la galería Leo Castelli. Con un lenguaje latino singular Ferrer causa un gran impacto en el mundo del arte internacional.

En 1981 Ferrer visita por primera vez a Las Terrenas en la República Dominicana lugar donde eventualmente construye un estudio. Comienza a pintar sobre lienzo personajes de clubes nocturnos, músicos, bailarines, etc. Luego directamente de la naturaleza crea paisajes saturados de colorido tropical. En estos momentos Ferrer continúa con intensa energía su búsqueda del paraíso perdido, una búsqueda que paradójicamente lo acerca cada vez más a un Puerto Rico que ya no existe —el Puerto Rico de su niñez. Ferrer es, en las palabras de la crítica Marimar Benítez, "el artista puertorriqueño de más trascendencia en el mundo del arte".

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Mirada a Nuestro Pasado - Hace 50 Años...

Cuando hace unos meses la Junta Editora del Boletín discutía la necesidad de obtener un mayor número de artículos de valor para nuestras próximas ediciones, se nos ocurrió la idea (ciertamente no original) de preparar una serie de trabajos sobre la historia de la medicina en Puerto Rico. Ya en el pasado compañeros como los Dres. Arana Soto, Torres Gómez y Rigau Pérez, entre otros, han hecho importantes aportaciones en esta área. Sin embargo, pensamos que esta serie que comenzamos con esta edición, más que un estudio de investigación profunda sobre nuestra historia, debiera de ser el reflejo de ésta según quedó retratada en nuestro propio Boletín hace cincuenta años.

Durante su larga historia, el Boletín de la Asociación Médica de Puerto Rico ha sido no sólo un rico caudal de información científica, sino que a la vez, al haber recogido en sus páginas notas biográficas, informes de comisiones, editoriales y cartas de nuestros médicos, nos brinda una oportunidad extraordinaria de ubicar a nuestra profesión con sus preocupaciones, problemas y logros en el marco más amplio de nuestra historia de pueblo.

En el 1938 presidía nuestra Asociación el Dr. José C. Ferrer. El Dr. Oscar Costa Mandry era su vicepresidente, el Dr. José Chavez su secretario y el Dr. Antonio Ortiz su tesorero. La Asociación Médica de Puerto Rico contaba con 329 miembros activos que eran "la gran mayoría de los médicos de Puerto Rico." Hubo durante ese año 39 ingresos, mientras murieron 5 socios y 37 fueron dados de baja por no pagar sus cuotas.

La Junta Editora de Boletín estaba compuesta por los doctores E. Martínez Rivera, Leopoldo Figueroa, Pedro S. Malaret, David García, J. Noya Benítez y Gaetan Roberts.

Nuestra Asociación tenía entre otras, Secciones de Tuberculosis, Cáncer, Mortalidad Infantil, Legislación, Hospitales, Seguro Médico e Historia de la Medicina.

En su informe sobre el año 1937, el presidente saliente, doctor J.H. Font, se quejaba de que los Comités "no trabajan", que la construcción del cuartel de la policía limita la expansión lateral de nuestro edificio, y pide la creación de un fondo para evitar "el triste espectáculo de las recolectas para ayuda a las viudas de los médicos."

El doctor García en un informe nos dice que se adquirieron durante el 1937, "Un balopticon" (proyector de clisés y fotos) a un costo de \$174.68, una "pantalla con cortina de pana", "megatiscopio con facilidades para aguantar tres placas al mismo tiempo" y un atril en ciprés para conferenciantes.

En marzo de 1938 se publicó un artículo por el Dr. Antonio Fernós Isern sobre las enfermedades cardiovasculares en Puerto Rico, las cuales ocupaban el séptimo lugar como causa de muerte, siendo la diarrea y

la enteritis la causa #1, la tuberculosis la #2, las enfermedades renales #3, la malaria #4 y la pulmonía la quinta.

El Coronel A.T. Cooper, M.C. US Army, publicó un artículo sobre el tratamiento de la tuberculosis, que consistía en "Controlled and regulated exercise, open air life, nutrition, collapse therapy, and building the patient up with exercise and cautious use of heliotherapy."

El incomparable Dr. Ramón Suárez, publicó durante el 1938 tres interesantísimos artículos en temas tan variados como "Experiencia con el Digital (Digilanida)", "Aplasia e Hipoplasia de la Médula Osea" y "Mieloma Múltiple".

Cuando acometimos esta empresa no teníamos idea del tesoro tan extraordinario que encontraríamos en las páginas del Boletín publicado en el 1938. Confirmamos el dictum de que la historia se repite, al ver que muchas de nuestras preocupaciones e inquietudes de hoy, que creíamos tan nuevas y originales, eran prácticamente las mismas de nuestros predecesores. Así como reconocimos muchas similitudes, también nos percatamos de las inmensas diferencias y cambios en la práctica de nuestra profesión en este lapso de tiempo, que obedecen mayormente a la limitada tecnología y farmacopea de aquellos distantes tiempos y a las prioridades dictadas entonces por enfermedades que hoy ya han prácticamente desaparecido o contra las cuales tenemos recursos que en el '38 no existían.

En este primer artículo hemos querido muy someramente hacer mención de algunas de las cosas que más nos llamaron la atención y que creemos pudieran despertar la nostalgia en algunos de ustedes y el interés en todos por conocer algo de nuestro pasado honroso y de aquellos colegas sobre cuyos hombros descansa nuestra generación. En artículos subsiguientes pediremos a distinguidos colegas que analicen trabajos de extraordinario valor o interés aparecidos hace cincuenta años señalándolos, cuando así sea apropiado, la evolución del campo en cuestión, en este medio siglo.

Bernardo J. Marqués, MD, FACR

Case Presentation

Lupus Anticoagulant and Waldenstrom's Macroglobulinemia

Norman Maldonado, MD, FACP
Anarda González, MD
Salomón Asmar, MD
Francisco Robert, MD, FACP
Mercedes Cruz Vidal, MD
Luis Fraguada, MD*

Summary: Prolongation of all phospholipid dependent coagulation test was found in a 62 year old woman with a dermal lymphocytic infiltrations but not associated with bleeding or thrombotic complications. She was found to have a IgM lambda monoclonal gammopathy with decrease in serum IgG and IgA. Peripheral blood and bone marrow studies were normal initially. A biologic false positive serology was detected. Extensive workup for an infectious or autoimmune disease was negative. Fever and splenomegaly developed and splenectomy was done. Light microscopy studies showed a plasmacytic neoplasm. Immunoperoxidase stain showed lambda light chains in the abnormal cells and EM studies confirmed the plasmacytic nature of the tumor. Flow cytometry of peripheral blood showed most cells with IgM and lambda light chain markers. A complete coagulation workup showed prolongation of the PT and PTT even when mixed with normal plasma. The thrombin time, platelet aggregation studies and bleeding time were normal. The tissue thromboplastin inhibition test was abnormal. The platelet neutralization test showed correction when platelets were used instead of phospholipids as the reagent, confirming the presence of a lupus anticoagulant. The site of production of the abnormal protein was confirmed by immunohistochemical techniques. The lupus anticoagulant was neutralized with goat antihuman IgM antisera confirming the IgM nature of the antibody.

The lupus anticoagulant has been described in systemic lupus erythematosus, other autoimmune disorders, drugs, neoplastic diseases, recurrent abortions, and the immunodeficiency syndrome. Our patient had a lymphoplasmatic disorder producing an IgM which was the lupus anticoagulant.

In 1952 Conley and Hartmann described a hemorrhagic disorder caused by a circulating anticoagulant in patients with systemic lupus erythematosus.¹ Since then the condition has been described in various

other diseases.^{2, 3, 4, 5} It has also become evident that the "lupus anticoagulant" is more frequently associated with thrombotic disorders rather than with bleeding.⁶ In most patients with lupus erythematosus the clotting inhibitor is of a different nature, that causes bleeding due specifically to antibodies against various clotting factors, especially factor VIII.

The "lupus anticoagulant" is characterized by impairment of the conversion of prothrombin to thrombin and prolongation mainly of the partial thromboplastin test and to a lesser degree the prothrombin time. The anticoagulant has been shown to be an immunoglobulin either IgG or IgM that acts *in vitro* by inhibition of the activity of phospholipids in clotting reactions.⁴ In 1980 Thiagarajan, Shaphiro and De Marco⁷ reported a patient with macroglobulinemia and a "lupus like anticoagulant" whose purified monoclonal IgM paraprotein showed the anticoagulant activity.

We are reporting a patient with Waldenstrom's macroglobulinemia who presented with skin lesions and marked prolongation of the partial thromboplastin time. She was found to have a lupus anticoagulant. The specialized laboratory studies, clotting tests, management during surgery and response to chemotherapy will be presented. Electron microscopic studies, histochemistry and flow cytometry studies were carried out.

Case Presentation

A 62 year old single Puerto Rican woman, retired school teacher, presented with an area of redness, induration and increased temperature in a lower extremity in January 1986. She had joint pains and allergies for years. There were no adenopathies or visceromegaly originally. The laboratory showed a hemoglobin of 14.8 gm/dl, WBC 5,360/mm³ with 73% neutrophils, 19% lymphocytes and 5% eosinophils. The urinalysis was normal. A partial thromboplastin time was 95 seconds and the prothrombin time was 14.8 seconds. A mixture with normal plasma failed to correct the prolongation of the clotting tests even after incubation for 1 hour. A serum protein electrophoresis showed a small monoclonal spike that proved to

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be an IgM by immunoelectrophoresis. Quantitative immunoglobulin levels showed IgG 450 mg/100 ml, IgA 89 mg/100 ml and IgM 3,200 mg/100 ml. The VDRL was positive in dilutions of 1:256. A bone marrow aspiration was non diagnostic. A lymphoproliferative process was suspected but could not be proven. The skin condition cleared after 3 weeks with IV vancomycin. The patient was followed in the clinics and found to have a subcutaneous nodule in the suprapatellar region which was biopsied and reported as lipogranulomatosis. The skin conditions recurred and this time failed to respond to vancomycin. The lesion was biopsied and reported as lymphocytic dermatitis. She was given saturated solution of potassium iodide (SSKI) by the dermatologist and the lesion cleared dramatically. However, in a few days she developed fever and the spleen became palpable. She was hospitalized and a complete work up was done. The Hgb was 11.5 gm/dl, the WBC was 11,000/mm³ with 74% segmented, 26% lymphocytes and the platelets 543,000/mm³. A urinalysis was normal with no proteinuria. The serum protein electrophoresis and immunoglobulins had not changed. Complement fragment C₃ was 114 mg/dl. The VDRL continued positive and anticardiolipin antibodies were present. The latex fixation, ANA, anti DNA and anti SSA were normal. Cryoglobulins and cold agglutinins were negative. Blood, urine, and throat cultures showed no growth. A viral profile showed a herpes I titer of 1:320 but otherwise was normal including the cytomegalovirus titer. SSKI was discontinued and the fever decreased. She was discharged improved.

Three months later she presented with spiking fevers, night sweats and progressive splenomegaly; the PTT and PT were very prolonged. The bleeding time was 5'. She was hospitalized and the laboratory studies were repeated. She was found to have a Hgb of 9 gm/dl. The other studies were unchanged. Febrile agglutinins, blood, urine and bone marrow cultures for bacteria, fungi, and acid fast were taken and reported normal. A CT scan of the abdomen showed only marked splenomegaly. The bone marrow repeated for the third time showed eosinophilia but was otherwise non diagnostic. Anemia required packed red cell transfusions twice. Coombs' test and reticulocyte count were normal. A trial with prednisone was given but after one week the fever recurred and she developed tachycardia and frequent premature ventricular contractions. Indomethacin was given with only transient control of fever. It was decided to perform an exploratory laparotomy and splenectomy after Pneumovax was given.

At laparotomy there was no bleeding. A large spleen and some large nodes were removed. The pathology showed immature lymphoplasmacytic and plasma cells. Imprints showed cells consistent with a plasma cell neoplasia. Immunoperoxidase showed positive staining for lambda light chains. Electron microscopy showed neoplastic cells with plasmacytic features.

The postoperative course was uneventful but in a few days she developed fever. Chemotherapy with cyclophosphamide, vincristine and prednisone (COP) was given with transient response. After 2 courses she still had fever and required hospitalization. She was found to have bilateral pulmonary infiltrates that progressed and were unres-

ponsive to mezlocillin, amikacin, erythromycin and trimethoprim sulfa (TMX). She became hypoxic with a PO₂ of 55 mm of Hg and hypercapneic with a PCO₂ of 52 mm Hg. The pH was 7.48. The EKG showed tachycardia, marked T wave inversions in VI-V3 and non specific ST changes. In a short time she became lethargic due to cardiac and respiratory failure. The urine showed proteinuria of up to 78 mg per dl that proved to be lambda light chains. The serum calcium increased to 12.5 mg per dl, the urea nitrogen was 74 mg per dl and the creatinine 1.6 mg per dl. A Swan-Ganz catheter was placed to monitor her cardiovascular status. The peripheral blood showed a marked leucocytosis of 48,000 with 49 segs and many lymphoplasmacytic cells some of which were immature. It was considered that she had a leukemic phase of her plasma cell dyscrasia with cardiac and pulmonary involvement. Chemotherapy with vincristine, adriamycin, dexamethasone (VAD) protocol was started. She received dexamethasone 40 mg daily, IV in divided doses, adriamycin 10 mg and vincristine 4 mg daily for four days by continuous infusion thru a central catheter. In a few days the patient began to improve. Fever decreased, blood gases normalized, the electrocardiographic changes reverted to normal and the pulmonary infiltrates cleared. Hypercalcemia and azotemia also improved. She gradually regained consciousness. Dexamethasone and trimethoprim were given from days 9 to 13 and 17 thru 21. She developed a neuropathy and vincristine was omitted from subsequent treatments. She continued to have low grade fever when off the chemotherapy or the dexamethasone. The lungs cleared with interstitial residual changes and also bronchiectasis requiring bronchodilator therapy. The partial thromboplastin time remained prolonged at 60 seconds and the prothrombin time 20 seconds. The urine protein decreased to 2.0 mg/dl and no light chains were detected on electrophoresis. The bone marrow had 20% lymphoplasmacytic cells not previously present. The patient required periodic packed red cell transfusion and modifications of chemotherapy. She received melphalan and prednisone in 2 cycles. The patient was hospitalized for transfusion and had an unexpected death while asleep. No autopsy was performed.

Material and Methods

Coagulation Studies

Routine coagulation studies were done by standard techniques using rabbit brain thromboplastin for the one stage prothrombin time and micronized silica and rabbit brain phospholipid as plasma activators for the activated partial thromboplastin time.

Demonstrations of Lupus-type coagulation inhibitors: Mixing studies were done with equal volumes of patient and normal plasma after incubation at 37°C for 0 to 60 minutes. The tissue thromboplastin inhibition test was done on plasma at thromboplastin dilutions of 1/100 and 1/1000. The platelet neutralization was done with freshly washed normal platelets suspensions as reported by Triplett.⁸ The plasma was treated with an IgM inhibitor

using a goat antihuman antiserum from sigma in an attempt to confirm the nature of the anticoagulant.

Platelet aggregation studies: These studies were done in platelet rich plasma adjusted to a platelet count of 300,000/mm³ with platelet poor plasma according to the method of Born and Cross.⁹ Adenosine diphosphate, epinephrine, and collagen were used as aggregating agents.

Electron Microscopic Studies

The buffy coat was fixed in 2.5% glutaraldehyde in phosphate buffer with glucose for a minimum of three hours. The material was post fixed with osmium tetroxide for 1 hour then dehydrated with different grades of reagent grade acetone and embedded in Epox 812. Thin and ultrathin sections were cut in an LKB ultramicrotome with a diamond knife, picked up in copper grids and stained with uranyl acetate and lead citrate. The sections were examined in an RCA EMU-3G electron microscope.

Flow Cytometry

Peripheral venous blood was obtained in heparin anticoagulant. The coulter procedure was used for the preparation of the mononuclear cell suspension. A Coulter Corporation flow cytometer model EPICS 541 system was used and monoclonal antibodies were obtained commercially from Coulter Immunology in Hialeah, Florida. Routine procedures for indirect immunofluorescent staining with monoclonal antibodies were used.

Results

Anticoagulant Studies

The coagulation results are shown in Table 1. The activated partial thromboplastin time was markedly prolonged in more than 30 different occasions and did not decrease significantly with splenectomy or chemotherapy. The prothrombin time was always prolonged but to a lesser degree than the partial thromboplastin time. The thrombin time was normal.

The mixing studies showed that the defect in coagulation occurred immediately with no significant potentiation with incubation for 1 hour. The tissue thromboplastin inhibition studies were prolonged at the

1:100 and the 1:1000 dilution with a ratio of 2.9 to 3.2 respectively when the normal ratio is less than 1.1. The platelet neutralization test showed a dramatic correction when a suspension of washed normal platelets were incubated with the mixture in this activated partial thromboplastin time. The control showed no change. The mixture of patients plasma with anti IgM antiserum showed a shortening of the PTT but especially of the prothrombin time as shown in Table II.

Table II

Immunologic Cell Markers		
MoAb	%PBL*	Normal Values % x MoAb
Kappa	15.53	
Lambda	25.07	
B ₄	11.45	10±5
T ₁₁	12.62	73±7
HLA-Dr	26.26	11±4
CALLA	6.40	2-6
IgM	51.82	5.8
IgG	12.49	4.0

*Peripheral blood lymphocyte.

Platelets Studies

The platelet count was normal or high. The simplate bleeding time was normal. The platelet aggregation studies response to adenosine diphosphate, epinephrine and collagen were normal with no evidence of defective coagulation or qualitative platelet disorder.

Light and Electron Microscopy

Spleen and lymph node histologic sections showed infiltrations with large mononuclear cells with excentric nucleus characteristic of lymphoplasmacytic neoplastic disorders. (Figure 1)

The special electron microscopic studies showed that the spleen and nodes were replaced with cells having plasmacytic features with eccentric nuclei, cart wheel chromatic pattern and abundant stacks of rough endoplasmic reticulum. (Figure 2)

Immunoperoxidase revealed positive staining for lambda light chains in the neoplastic plasmacytic cells.

Table I

Laboratory Assesment of Coagulation Parameters		
Coagulation Assays	Patient	Normal Values
Prothrombin time (PT)	22.3 sec	10.9 - 13.3 sec
Activated partial thromboplastin time (PTT)	71.5 sec	22.7 - 36.7 sec
Circulating anticoagulant Screening		
PT (50:50)	20.5 sec	
PTT (50:50)	67.5 sec	
Tissue thromboplastin Inhibition (Dilution/Ratio)*	1:100 /2.9	1.3
	1:1000/3.2	1.3
Platelet neutralization procedure (PNP)*		
Control saline	74.8 sec	
PNP	43.8 sec	

*Reference No. 8

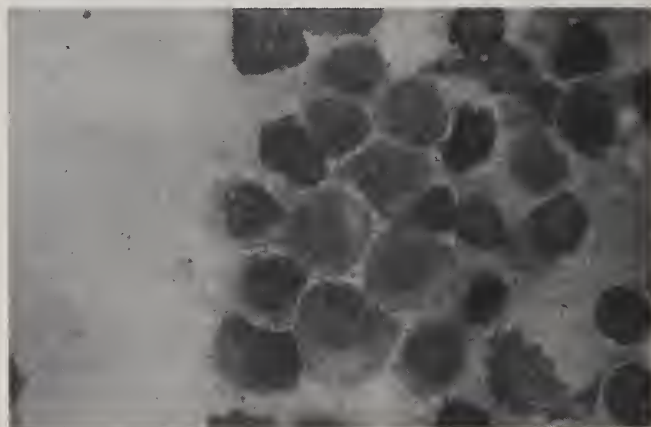


Figure 1. Imprint from lymph node obtained at laparotomy showing cells with excentric nuclei with blue cytoplasm suggestive of plasma cells.

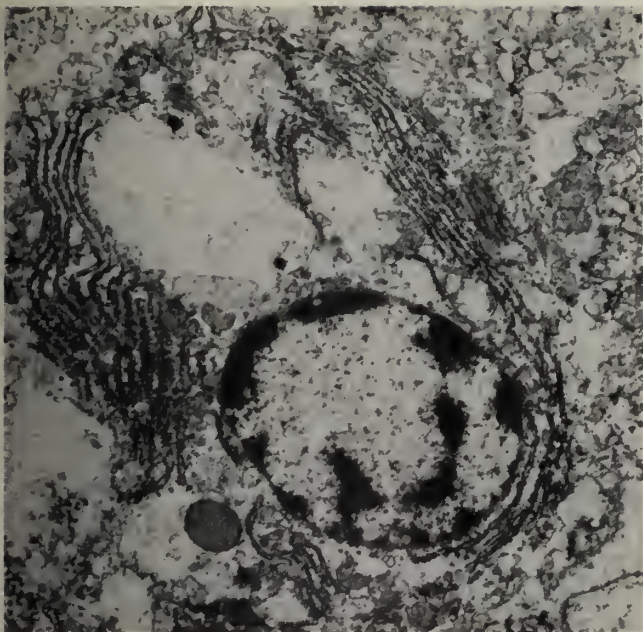


Figure 2. Cells with abundant cytoplasm studied with rough endoplasmic reticulum, nuclear peripheral condensations of heterochromatin and prominent nucleolus. This cell resembles a plasmacytic cell.

Flow Cytometry

The flow cytometry results showed that IgM positive cells were 10 times the normal value confirming the impression of Waldenström's macroglobulinemia. There was an inversion of the kappa and lambda ratio which is usually 2:1 or 3:1 to a 1:2 ratio. The T-11 cells were markedly depressed. See Table II.

Serum and Urine Protein Studies

Immunoglobulin done originally were: IgG 450 mg/dl, IgA 89 mg/dl, IgM 3,706 mg/dl. Immunoelectrophoresis showed an IgM monoclonal gammopathy and increase lambda light chains. IgG was decreased. The urine showed a spike in the gamma region which was shown to be lambda light chains.

Subsequently with the onset of renal insufficiency, hypercalcemia and albuminuria, other fractions appeared. After chemotherapy the urine protein decreased to 2 mg/dl, a small amount of albumin. The serum immunoelectrophoresis did not change significantly with treatment even though the total amount of IgM decreased to 1,200 mg/dl.

Discussion

The lupus anticoagulant is a spontaneously acquired anticoagulant initially described in patients with systemic lupus erythematosus but subsequently has been described in patients with other autoimmune disorders,¹⁰ in association with drugs,¹¹ in neoplastic conditions^{2, 3} and in patients with no underlying diseases.^{2, 3} The neoplastic diseases found associated with the lupus anticoagulant include carcinomas, lymphomas, and multiple myeloma.³ In more recent years the association of frequent abortions and lupus anticoagulant has been made.¹² The

acquired immunodeficiency syndrome has also been associated with this phenomenon.¹³

In 1974 the association of a biologic false positive serologic test for syphilis in a patient with Waldenström's macroglobulinemia was made by Drussin.¹⁴ In this same year a monoclonal IgM with antibody specificity for phospholipids was reported in a patient with lymphoma by Cooper.¹⁵ In 1975 a patient with Waldenström's macroglobulinemia was described in which an antibody with specificity against phosphorylcholine was found.¹⁶ In none of these patients was prolongation of coagulation tests described.

In 1980 Thiagarajan, Shapiro and De Marco reported their study of the mechanism of a lupus anticoagulant in a patient with macroglobulinemia.⁷ This patient had a prolongation of all phospholipid dependent coagulation tests with no bleeding manifestations. The purified monoclonal IgM lambda protein and its Fab mu tryptic fragment induced similar changes in normal plasma. The patient's lambda paraprotein reacted with anionic phospholipids such as phosphatidylserine, phosphatidylinositol and phosphatidic acid but not with neutral phospholipids such as phosphatidylcholine and phosphatidyl ethanolamine. Prior incubation of phospholipids with the patient's Fab mu blocked the reaction. Substitution of washed platelets for phospholipid led to normalization of the coagulation test and corrected all abnormalities produced in normal plasma by the patient's IgM. These studies support the concept that platelets and not phospholipid micelles are the primary locus of prothrombin and Factor X activation in normal hemostasis. This same mechanism was confirmed in 5 patients with IgG lupus anticoagulant in patients with lupus-like syndromes and thrombosis.¹⁷

In a study of 219 subjects with a lupus anticoagulant, Gartineau et. al found 153 who had protein electrophoresis done and 11 had monoclonal gammopathies.¹⁰ Two patients had multiple myeloma and two lymphoproliferative disorders.

Platelet aggregation studies were normal in our patient. This is in contrast to the reports of some of AIDS patients who were found to have platelet aggregation defects in addition to the lupus anticoagulant.¹³ In these group of patients opportunistic and acute infections seemed to be a triggering mechanism for the disorder. Bleeding was present because of the platelet disorder and needed treatment in contrast to all the other patients with lupus anticoagulant who do not bleed and have an increase incidence of thrombosis.⁶

Our patient is the second reported patient to our knowledge with a plasma cell disorder of the Waldenström's macroglobulinemia type to present with a lupus anticoagulant. Like most patients she had no bleeding tendencies and underwent splenectomy with no bleeding problems. She also developed pulmonary and cardiac involvement by the lymphoplasmacytic disorder as has been reported previously.^{17, 18, 19} Response to therapy was partial even with an aggressive regimens and the lupus anticoagulant did not disappear.²⁰ The IgM macroglobulin was shown to be present in neoplastic cells by immunoperoxidase staining. Flow cytometry confirmed the increase number of IgM positive cells with inversion

of the kappa and lambda ratio. The lupus anticoagulant was neutralized using anti IgM antisera and the prothrombin time improved as compared to the control. This confirmed the IgM nature of the lupus anticoagulant in our patient.

Resumen: Una prolongación de las pruebas de coagulación dependientes de fosfolípidos fue detectada en una paciente de 62 años con una dermatitis linfocítica, pero que no tenía problemas de sangría ni trombóticos. Se detectó una gamapatía monoclonal de tipo IgM lambda con hipoglobulinemia IgG e IgA. La sangre periférica y la médula ósea eran normales inicialmente. La serología fue falsa positiva confirmada por la prueba de anticardiolipina. Todos los estudios para enfermedades infecciosas o autoinmunes fueron negativos. La paciente desarrolló fiebre y esplenomegalia por lo que se le practicó una esplenectomía. La histología demostró un neoplasma plasmático. La inmunoperoxidasa demostró cadenas lambda en las células anormales y la microscopía electrónica confirmó el origen plasmático del tumor. La citometría de flujo en sangre periférica demostró la mayor parte de células IgM y con marcadores lambda. La coagulación demostró la prolongación del PT y PTT aún con mezcla de plasma normal. La prueba de inhibición de tromboplastina de tejido fue anormal. La prueba de neutralización de plaquetas demostró corrección cuando se usó plaquetas en vez de fosfolípidos como reactivo, confirmando la presencia del anticoagulante de lupus. El lugar de producción de la proteína anormal fue confirmado por estudios inmunohistoquímicos. El anticoagulante de lupus fue neutralizado con un antisuero anti IgM confirmando la naturaleza del anticuerpo.

El anticoagulante de lupus se ha descrito en varias enfermedades especialmente el lupus eritematoso, pero también en otras enfermedades autoinmunes, uso de medicamentos, enfermedades neoplásicas, abortos recurrentes, y el síndrome de inmunodeficiencia adquirida. Nuestro paciente tenía un desorden linfoplasmático produciendo hiperglobulinemia M que a su vez era el anticoagulante de lupus.

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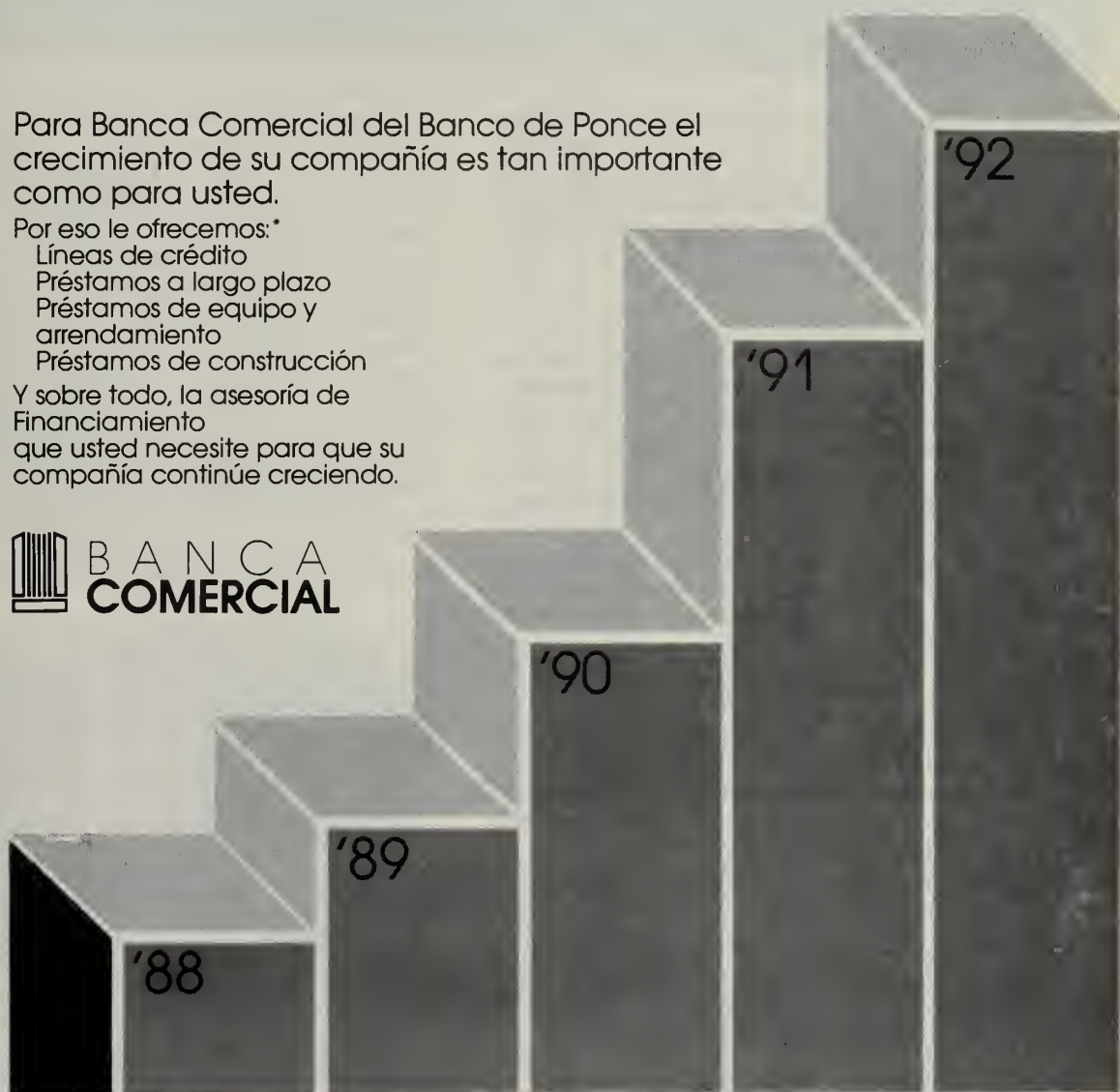
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Microcystic Adenoma of the Pancreas: Report of a Case and Review of the Literature

Carlos Balsalobre, MD
Manuel A. Marcial, MD
Raúl A. Marcial-Seoane, MD
Víctor Collazo, MD
David Rodríguez-Pérez, MD

Summary: The case of a 79-year-old female with a microcystic adenoma of the pancreas is reported. The clinical, radiological and pathologic findings of this case are presented and compared with previously published cases. The differential diagnosis, prognosis and therapeutic recommendations for this entity are discussed.

Cystic neoplasms of the pancreas are classified as either microcystic adenoma (serous cystadenoma) or mucinous cystadenoma.^{1, 2} These two recognizable neoplastic entities, although extremely uncommon, differ markedly in prognosis and in therapeutic recommendations, thus making knowledge of their differential diagnosis essential for their adequate management. While microcystic adenoma, also known as glycogen rich cystadenoma, is a completely benign lesion, mucinous cystadenoma is considered a malignant or potentially malignant neoplasm.^{1, 2}

Report of a Case

A 70-year-old thin white female was well until a few months prior to admission when she developed diffuse abdominal discomfort that eventually became painful and was accompanied by a 15 pound weight loss. She discovered a right upper quadrant mass on self examination. She denied intolerance to fatty foods and had not experienced changes in bowel habits or melena. She documented an occasional oral temperature of 38°C, but denied chills or sweats. She denied a history of jaundice, liver disease, itching or rash. There was a history of river bathing. The patient denied alcohol abuse.

On physical examination her blood pressure was 110/70 mm Hg, pulse rate 60/min, respiratory rate 12/min and oral temperature of 38°C. The patient was oriented in time, person and space and was not in acute pain. Aside from the abdominal findings, her physical examination was entirely normal.

Abdominal examination revealed no bruits or thrills. On palpation a firm mass was noted in the right upper quadrant. Peristalsis was normal. Laboratory tests,

including a serum chemistry profile, a complete blood count, protein electrophoresis, and urinalysis, were within normal limits. The patient had a negative hepatitis B surface antigen test, normal levels of alphafetoprotein and a serum carcinoembryonic antigen level of 8.0 ng/ml (normal less than 3 ng/ml).

Radiological findings included transverse and longitudinal ultrasound images of the upper abdomen showing a 10 cm. nodular mass in the head of the pancreas. (Fig. 1) The mass was predominantly cystic with good sound transmission through the lesion. There were many bright linear echoes within the mass lesion. Such sonographic images are consistent with the presence of multiple small cysts, each thin septum leading to an echogenic signal. A computed tomographic (C.T.) scan without contrast revealed a nodular mass of low attenuation density in the head to the pancreas.

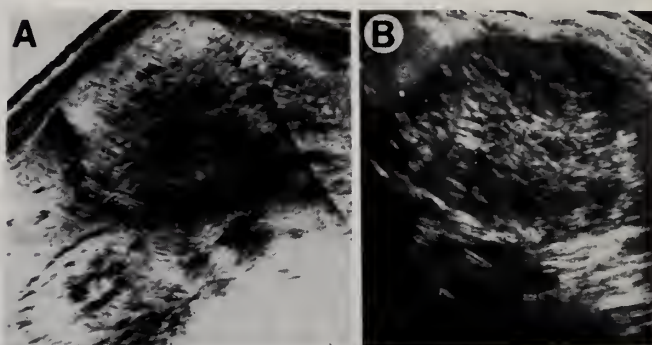


Figure 1. Transverse (A) and longitudinal (B) ultrasound images of the complex mass in the head of the pancreas. The lesion shows many bright internal echoes corresponding to the walls or septa of the multiple tiny cysts which make up the mass.

(Fig. 2-A) After the administration of intravenous contrast there was enhancement of the margins and internal septations of the mass. (Fig. 2-B) A central stellate scar with radiating bands of connective tissue was suggested by the CT image. (Fig. 2-C)

The patient was taken to the operating room for an exploratory laparotomy. A right paramedian incision was performed and a multilocular cystic pancreatic mass was found. The mass was compressing and deforming the vascular, biliary and duodenal conduits. (Fig. 3) The mass was biopsied and cholecystectomy, choledocoe-

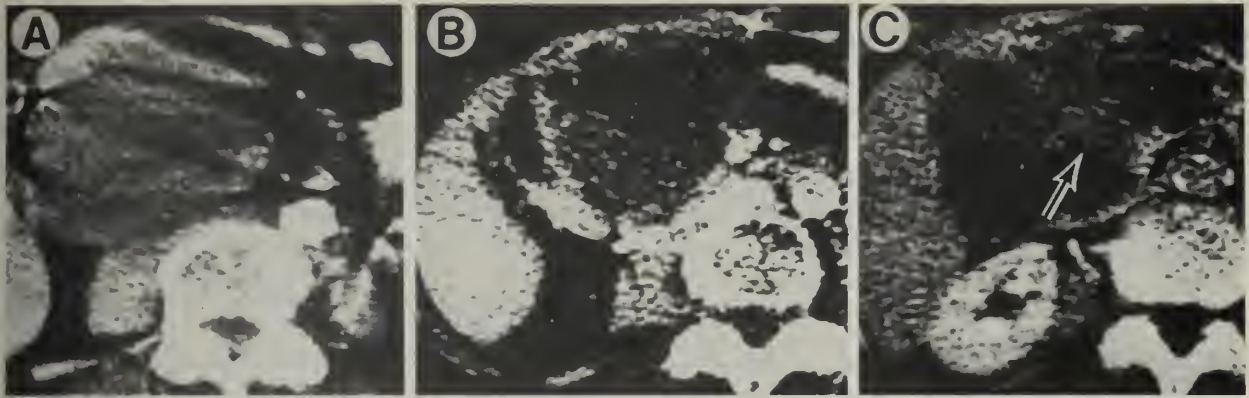


Figure 2. A) Computed tomography reveals a large, well defined mass of low attenuation density. B) Post-contrast CT scan shows enhancement of

the internal septa. C) CT scan reveals a central stellate scar (arrow) within the mass.

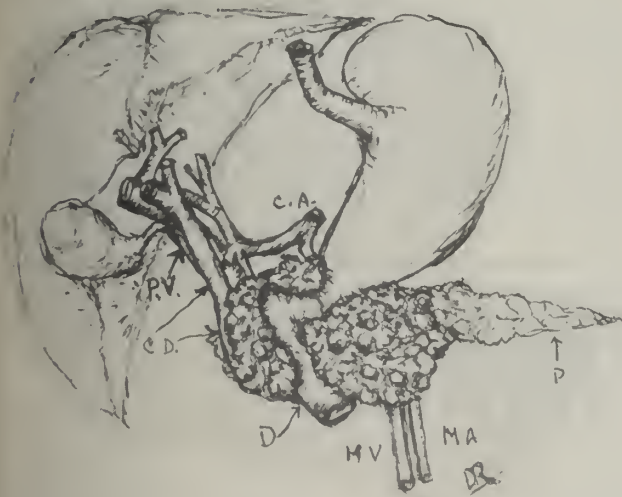


Figure 3. Schematic diagram of the operative findings. D) Duodenum deformed by the cystadenoma. CD: Common duct displaced and partially surrounded by tumor. PV, MV, and MA: Portal and superior mesenteric vessels surrounded by tumor. CA: Celiac axis P: Normal tail of the pancreas.

junostomy and gastrojejunostomy were done. The patient recovered from the operative procedure and except for a feeling of abdominal fullness, due to residual tumor, was asymptomatic. She died eight years later of unrelated causes.

Postmortem examination revealed a well circumscribed mass in the head and body of the pancreas. The tumor displaced but did not infiltrate any of the surrounding organs. The liver was unremarkable. There were no enlarged regional lymph nodes. All the surgical anastomoses were patent.

The mass, which measured 12 x 10 x 8.5 cms., had a gray-tan, multilobular external surface. Multiple sections of the mass revealed a honeycombed cut surface with multiple, tiny cysts ranging in size from 0.1 to 1 cm. in diameter. (Fig. 4-A) The cysts were filled with clear yellow fluid. A central dense scar with radiating fibrous trabeculae was present. (Fig. 4-A)

Histologically the tumor had a spongy or alveolar appearance on low magnification. (Fig. 4-B) The multiple tiny cysts were lined by a single, flat layer of low cuboidal epithelial cells (Fig. 4-C) with only occasional

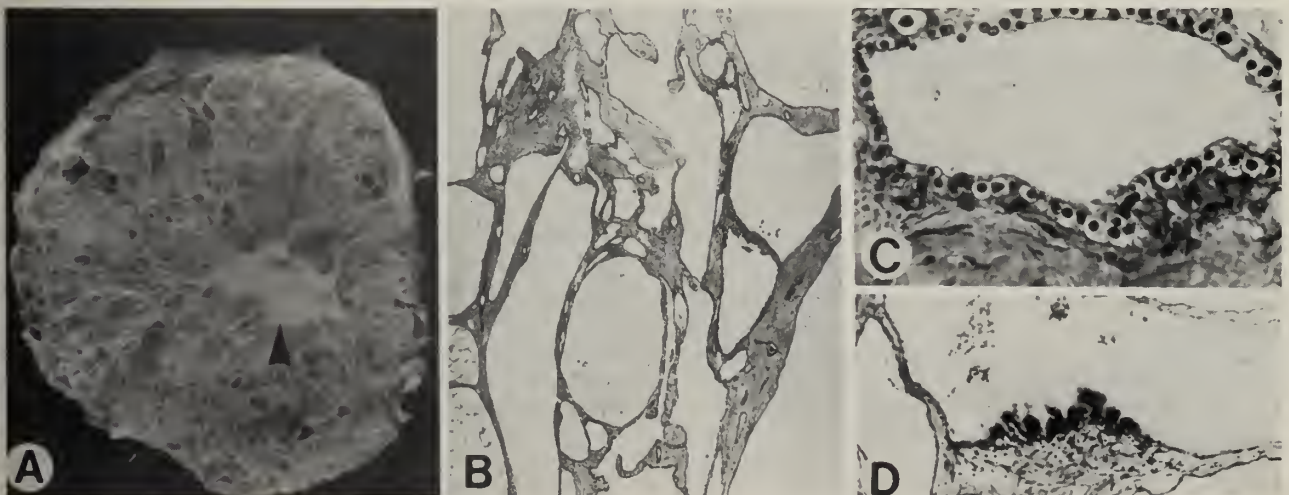


Figure 4. A: Gross photograph of the microcystic adenoma: Note the honeycomb appearance produced by the tiny cysts and the central stellate scar. (arrowhead)

B: Low magnification photomicrograph of the cystadenoma. Note

the alveolar pattern of the epithelial lined cysts.

C: Microcyst lined by a single layer of low cuboidal epithelial cells with clear cytoplasm.

D: Cyst with focal simple papillary projections.

intraluminal papillary projections. (Fig. 4-D) There were no mitotic figures, and the cells revealed no pleomorphism nor atypia.

Histochemical stains which included mucicarmine and Periodic Acid Schiff, demonstrated the presence of glycogen and the absence of mucin.

On the basis of the clinical history, gross findings and histopathologic features, a diagnosis of microcystic adenoma of the pancreas was rendered.

Discussion

Cystic neoplasms of the pancreas have traditionally been divided into cystadenomas and cystadenocarcinomas. Based on a large clinicopathologic study Compagno and Oertel classified these neoplasms into mucinous cystadenomas and glycogen rich microcystic adenomas.^{1, 2}

Microcystic adenomas, also called serous cystadenomas, are rare benign neoplasms of the pancreas that in some series account for less than 1% of all pancreatic tumors.³ This tumor occurs most often in women in their 7th. decade of life. (Table I) The most common initial signs or symptoms are: abdominal pain, the presence of an abdominal mass, back pain, icterus and weight loss. These tumors occur throughout the entire pancreas. Our survey of 53 reported cases did not reveal a predilection for the adenomas to localize to any particular anatomic site within the pancreas. (Table I)

Roentgenographic findings may include a mass seen in the upper abdomen with anterior displacement of the stomach and the transverse colon and inferior displacement of the left kidney.⁴ Occasionally there are calcifications. On CT and sonography, a multilocular cystic pancreatic mass, with or without calcifications, is usually described.^{5, 6} A stellate scar with radiating bands of connective tissue is very characteristic.⁶ Angiography usually demonstrates a highly vascular tumor.^{1, 6}

On gross examination, these tumors are well circumscribed and have an average size of 10 cm. The tumors are separated from adjacent parenchyma by dense fibrous tissue. On section, small cysts ranging from 0.1 to 2-3 cms. are separated by fine septa. The cysts contain a clear proteinaceous fluid and have smooth glistening walls. Microscopically, the cysts are lined by cuboidal and occasionally flattened epithelial cells with glycogen rich clear cytoplasm. Mitotic figures are absent, and there is no atypia. Simple papillary structures are occasionally seen. However, well formed papillae are usually absent.

The histogenesis of these tumors is still unclear. They have been classified as tumors arising from ductal epithelium or from centroacinar cells. Due to the presence of glycogen in fetal centroacinar cells, the latter origin is favored. Recent studies using immunocytochemistry and electron microscopic techniques lend support to the theory of the centroacinar cell being the cell of origin for this neoplasm.^{5, 7}

Microcystic adenomas of the pancreas are benign tumors. In none of the cases reported has there been evidence of metastases. The neoplasm has always remained circumscribed within the pancreas without invading adjacent organs. Thus if the patient is asymptomatic and a diagnosis of microcystic adenoma is made by biopsy, pancreatic resection is not necessary.^{1, 4} This is very important in the elderly and in other high risk groups where surgical risks may be greater than surgical benefits. Our case, with its 8 years follow-up, without complications nor malignant behavior is a clear example of this therapeutic approach.

According to Compagno and Oertel^{1, 2} mucinous cystadenomas comprise the remaining cystic neoplasms of the pancreas. Mucinous cystadenomas are unilocular or multilocular neoplasms. The large cysts are lined by columnar, mucin producing epithelium. Papillary formations, epithelial stratification and cellular pleomorphism and atypia are not uncommon. It is not unusual to find foci of carcinoma adjacent to areas lined by apparently benign epithelium. The demonstration of carcinoma then depends on the adequacy of sampling. This has also been the case for mucinous cystic neoplasms of the ovary and biliary tree.^{9, 10} Thus, mucinous cystadenoma of the pancreas is considered an overtly or potentially malignant neoplasm.² Therefore, if a cystic neoplasm of the pancreas is shown to be lined by mucinous epithelium a more aggressive surgical approach is recommended.

Table I

Summary of Clinical and Pathologic Data in 53 Cases of Microcystic Adenoma of the Pancreas

Age (yr.)	
Mean	: 68 years
Range	: 35-89
Sex	
Male	: 15
Female	: 38
Anatomic location	
head of pancreas	: 16
body of pancreas	: 4
tail of pancreas	: 15
body and tail	: 6
entire pancreas	: 5
junction of head and body	: 1
data not available	: 6
Size (cm)	
Mean	: 9.7 cm.
Range	: 1 cm. - 25 cm.

Resumen: Se reporta el caso de una mujer de 79 años de edad con el diagnóstico de adenoma microquístico del páncreas. Los hallazgos clínicos, radiológicos y patológicos son presentados y comparados con los de los casos previamente reportados en la literatura. Se discute el diagnóstico diferencial, pronóstico y las recomendaciones de esta entidad.

Acknowledgements

The authors are grateful to Dr. Alberto F. Fernández and Dr. Raúl A. Marcial Rojas for their critical review of the manuscript, and to Ana Acevedo for her skilled secretarial assistance. This work was supported by RCMI award RR-03055-01A1 from the National Institutes of Health.

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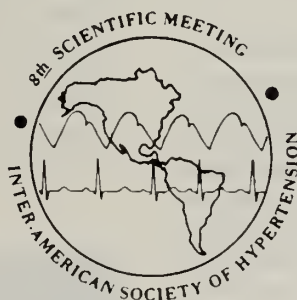
EDITORIAL COMMENT

Upon revision of the article by D. Rivera et al: *Neurological Disorders Associated to Dengue Infection*, *Bol Asoc Med P R* 1988; 80:208-211 following a letter received from Dr. Duane Gubler, the Editor finds there is a great similarity between the published article and Dr. Gubler's original paper delivered at the International Conference on Dengue at Kuala Lumpur.

There is an *ad verbatim* presentation of the tables as well as other information in the text. The Editorial Board and the authors wish to apologize to Dr. Gubler for this inadvertent use of the material without giving him full recognition for the original publication. They did however include the article by Dr. Gubler in the bibliography.

R.V.J.

VIII SCIENTIFIC MEETING INTER-AMERICAN SOCIETY OF HYPERTENSION

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SATELLITE SYMPOSIA

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Deadline for receipt of abstracts November 21, 1988

Notification of Abstract acceptance January 30, 1989

Deadline for pre-registration March 15, 1989

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Hepatotoxicity After Prolonged Use of Acetaminophen: A Case Report

Evelio F. Bravo-Fernández, MD*
K. Rajender Reddy, MD
Lennox Jeffers, MD
Eugene R. Schiff, MD

Acetaminophen is one of the most widely used over the counter analgesic and antipyretic in the United States. It is advertised as a safe and effective drug with few side effects when used in the recommended therapeutic doses. Even more, it is preferred over aspirin because it does not injure the gastric mucosa.

Liver damage associated with acetaminophen overdose is a well known problem in suicidal attempts.¹⁻² Recently hepatotoxicity has been reported after relatively low doses of acetaminophen in alcoholics.³ Also the association of chronic use of acetaminophen in doses of 2.9-8 gm. per day during a period of several weeks and the development of toxic hepatitis has been previously reported.⁴⁻⁵ Although unusual portal tract reaction are known to occur with acetaminophen.⁶ The classical histological picture is that of centrilobular confluent necrosis with a variable degree of cell loss and associated reticulin collapse.⁷

Here we report a case that is a good example of acetaminophen hepatotoxicity induced by self prescribed doses during a period of several months.

Case Report

A 48-year-old Cuban female was admitted to the University of Miami Jackson Memorial Hospital with a three week history of general malaise, anorexia, nausea, vomiting, dark colored urine and light colored stools. She also complained of a dull epigastric pain and right upper quadrant discomfort not associated with food and not alleviated with antacids. Sometimes, it was radiated into the back. There was no weight loss, history of hepatitis in the past, blood transfusion, intravenous drug abuse, alcohol intake, ingestion of uncooked clams or recent travels abroad. Upon further questioning, she accepts taking approximately 8-10 extra-strength acetaminophen capsules every day (4-5 gm.) during the last five months for headaches and bodyaches. On physical exam the vital signs were stable without evidence of orthostatism. Scleral icterus was evident, the lungs were clear to auscultation, the heart rate was regular and there was no gallop rhythm. There was tender hepatomegaly with a liver span of 10 cms at the right mid clavicular line. No hepatogastric reflux could be elicited. Spleen was not palpable.

Extremities showed mild pretibial edema and palmar erythema, no spider angiomas were seen on the skin.

The laboratory data at admission included: hemoglobin 15 g/dl, leukocyte count 9,500/mm and adequate platelets, prothrombin time 14.9 sec (control 11 sec), total serum bilirubin 26 mg/dl (normal 0.3-1.0 mg/dl), serum aspartate aminotransferase (AST) 739 U/L (normal 3-38 U/L), alanine aminotransferase (ALT) 570 U/L (normal 3-35 U/L) and alkaline phosphatase 258 U/L (normal 36-125 U/L). The serologic test for hepatitis A & B were negative. Acetaminophen blood level was 0.7 ug/l. Further laboratory evaluation revealed normal renal function, negative antinuclear antibody and anti mitochondrial antibody tests. A CT scan of the abdomen revealed hepatomegaly and normal bile ducts without evidence of focal hepatic lesions. No pancreatic tumor was seen. The patient was treated symptomatically and a liver biopsy was performed once the coagulation parameters improved with vitamin K therapy. It revealed the classical centrilobular necrosis associated with acetaminophen hepatotoxicity (See figure 1). In addition, expanded portal tracts with increased amount of fibrosis and regenerative nodule formation consistent with cryptogenic cirrhosis were detected in the biopsy (not shown in this picture). The patient had a significant symptomatic improvement and a tendency towards normalization of the transaminases and coagulation parameters, so she was discharged.

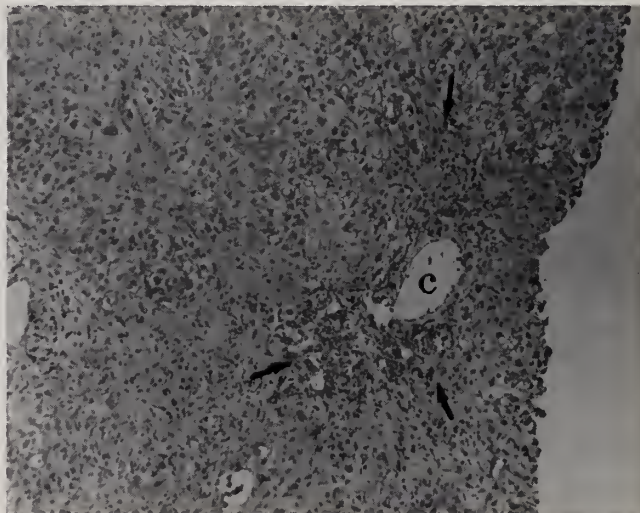


Figure 1. Percutaneous needle biopsy showing a zone of parenchymal necrosis (arrows) around the central vein (C), also some vacuolation of the hepatocytes may be seen. Hematoxylin & Eosin.

From the Center for Liver Diseases, Division of Hepatology, Department of Medicine, University of Miami School of Medicine Miami, Florida.

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Discussion

Acetaminophen, a widely used antipyretic analgesic, has an interesting metabolic pathway in the hepatocyte (See figure 2). Most of the drug is conjugated with glucuronic acid or sulphate and excreted in the urine.⁸ A minor amount of the drug undergoes metabolic oxidation by the cytochrome p-450 mixed oxidase system and is converted to a highly reactive electrophilic intermediate metabolite, which is preferentially conjugated with glutathione into a non-toxic metabolic (acetaminophen mercapturic acid) and excreted in the urine.⁹ In cases of massive overdosage, the amount of reactive intermediate metabolite is increased as the result of a greater amount of drug present in the liver and utilization of the glutathion storages. It is the reactive metabolite that mediates the toxicity by covalently binding nucleophilic proteins in the hepatocytes.² For this reason, the treatment of acetaminophen overdosage is directed to replenish the glutathion storage. This is possible by using

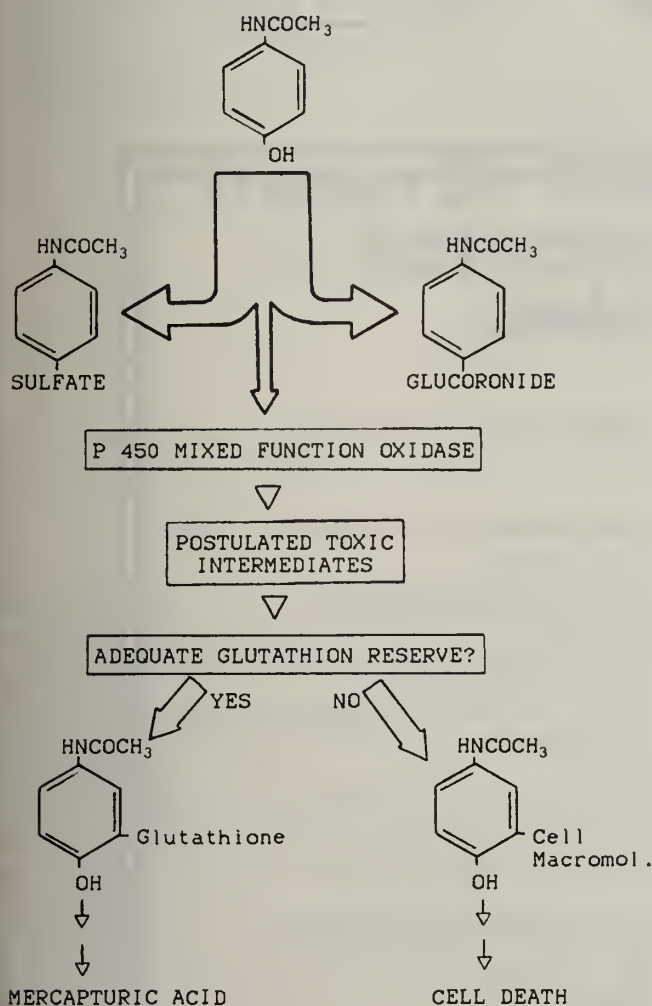


Figure 2. Metabolic pathways of acetaminophen. Note that the major metabolic pathways are by glucuronidation and sulfaction. A minor pathway leads to the formation of acetaminophen-mercapturic acid. In cases of overdosage the glutathion reserve may be exhausted with the consequent accumulation of the toxic intermediates which will covalently bound to the cell macromolecules, causing the cell's death.

N-acetylcystein in a loading dosage of 140 mg/kg given orally, followed by a maintenance dose of 70 mg/Kg every four hours thereafter, over a period of 68 hours for a total of 17 doses.² Its mechanism of action is believed to be the replenishment of the glutathion storages facilitating the metabolic detoxification of the intermediate toxic metabolite of acetaminophen. In our case N-acetylcystein was not given because by the time our service was consulted, the patient had been off the medication for more than 48 hours and the acetaminophen blood level was only 0.7 ug/ml, it was felt that at that point the treatment would not be necessary. But we believe that if plasma levels are not readily available, antidotal treatment should be started immediately. Once the plasma levels are confirmed to be in the nontoxic range, therapy may be terminated.

In the absence of hypotension and congestive heart failure, the role of acetaminophen ingestion in our patient's acute hepatitis is clear, given the classical centrilobular necrosis on the liver biopsy. But its role (if any) is uncertain in the etiology of the cirrhosis that our patient had. The possibility that acetaminophen, like methotrexate or alcohol, when used in large doses for a prolonged period of time could produce a chronic subclinical injury ultimately ending in cirrhosis is speculative. We believe that more likely, acetaminophen toxicity was superimposed on a cryptogenic cirrhosis.

It has been suggested that the toxic effect of this drug is enhanced by a low protein diet, perhaps mediated by diminished glutathion synthesis.¹⁰ Although this hypothesis has been challenged,¹¹ the possibility that this patient could have had reduced glutathion storages and thus be more susceptible to injury from acetaminophen can't be ruled out.

Whether patients with cirrhosis are at increased risk of developing acetaminophen toxicity is not completely clear at present. Until more is known about the metabolism of this drug in patients with chronic liver disease, physicians should be aware of the possible hepatotoxicity with the prolonged use of relative low doses and should not recommend the extra-strength (500 mg) formulation in patients with liver disease unless they are under close medical supervision.

Resumen: La toxicidad producida por la sobredosis de acetaminofen es un problema bien conocido en casos de intentos de suicidio con este medicamento. Se presenta un caso donde la paciente desarrolla sintoma y signos clínicos consistentes con una hepatitis aguda secundaria al uso prolongado de acetaminofen. Se discuten las características histológicas de la toxicidad hepática y el metabolismo de la droga en condiciones normales y en casos de sobredosis. También se menciona el tratamiento del envenenamiento por acetaminofen. Se recomienda no usar la preparación extrafuerte (500mg) en pacientes con enfermedad hepática a menos que están bajo estricta supervisión médica.

Acknowledgement

The authors wish to thank Waleska Galindez, M.D. Pathology Resident at VAH SJ PR and UPR School of Medicine for taking the microphotography and Mr. Jesus M. Ayala O'Neill (Illustrator) Medical Media VAH SJ PR for the art work.

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Fatal Repetitive Ventricular Tachycardia in a Child

Charles D. Johnson, MD, FACC

Summary: This article describes a repetitive ventricular tachycardia in a six-year-old boy, which led to his death, following a symptomatic course of palpitations, tonic seizures, loss of consciousness, cardiopulmonary arrests and ventricular fibrillation. Ventricular tachycardia in pediatric practice is reviewed, emphasizing the rare lethality of the idiopathic paroxysmal repetitive variant of ventricular tachycardia.

Ventricular tachycardia (VT) and its interesting, less well-recognized variant, "Idiopathic Repetitive Paroxysmal Ventricular Tachycardia" (IRPVT), have been encountered infrequently in pediatric practice. IRPVT has carried the reputation for a long-term benign prognosis, but incessancy and poor response to antiarrhythmic therapy. However, death rarely has complicated this particular variant of VT.¹⁻¹⁰

This communication describes a child who eventually demised with IRPVT, and reviews the reported experience with VT and this seldomly recognized subtype in pediatrics, remembering their potentially lethal nature.

Case Report

This 6-year-old male suffered from palpitations, malaise, abdominal pain, tonic seizures with loss of consciousness, and two episodes of cardio-respiratory arrest and ventricular fibrillation (Vf). The family history was not remarkable. The child was otherwise healthy and was not deaf. The cardiac examination was normal and there was no cardiomegaly.

An electroencephalogram, a computerized tomography of the head and an echocardiogram were normal. Serum potassium was 3.6 meq/L. Tocainide HCl, 300 mg. q. 6 h orally, was administered for the management of "VT".

However, his symptoms and cardio-respiratory arrest with seizures and Vf recurred, followed by death. Lidocaine was administered and defibrillation was applied at the terminal fatal event.

Unfortunately, an autopsy was not obtained. Elevated titers of Coxsackie virus were reported, and viral myocarditis was considered a possible but unproven diagnosis.

The intrinsic electrocardiogram (ECG) was normal except for inverted or diphasic T waves in leads V₁-V₆ (Figure 1). The cardiac rhythm was rarely stable (present

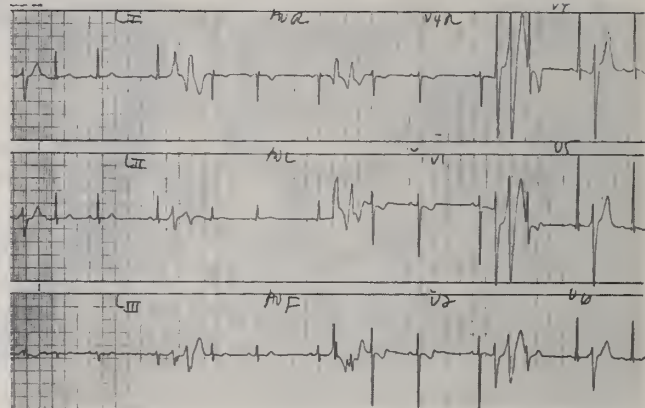


Figure 1. 12-lead electrocardiogram (ECG). There were T wave abnormalities in the periods of sinus beats of leads V₁-V₆. Single and/or coupled ventricular ectopy (VPB's), with R-on-T beats and multiformity at very rapid rates, occurred in all leads. A QR pattern was present in aVR and V₁, and a R/S pattern in lead V₆, but the morphologies varied. Some of the VPB's were interpolated with retrograde concealed conduction.

on a non-illustrated tracing). Figures 1-4 show a VT resembling repetitive paroxysmal VT (RPVT). There were recurrent salvos of broad QRS tachycardia, between which were interspersed brief periods of normal sinus rhythm and conduction. The QRS morphological pattern was bizarre and variable, and showed a tendency to left axis deviation. Atrioventricular dissociation was observed. The Q-T interval was not prolonged and the presentation was not classical for "torsade de pointes". There were

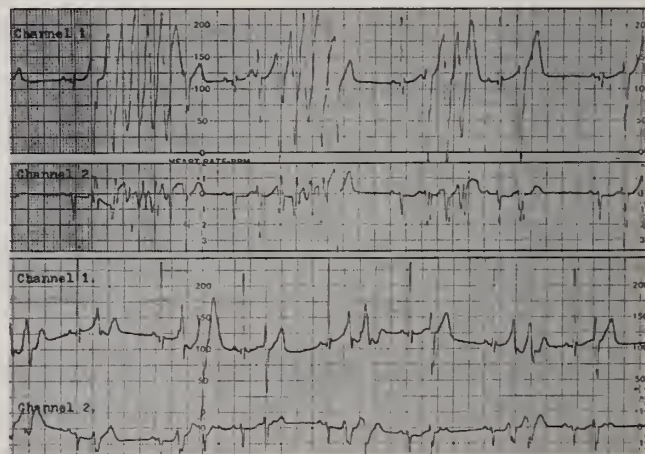


Figure 2. Holter ECG. Upper Panel, Channels 1 and 2; Lower Panel, Channels 1 and 2. These tracings showed the variable, bizarre morphologies of the VPB's and ventricular tachycardia (VT), probably indicating multifocal origin in the ventricles. Atrioventricular (AV) dissociation, and possibly ventricular fusion beats were present. There was slight tendency to twisting of the points in the upper panel, with extremely fast rates (375 bpm).

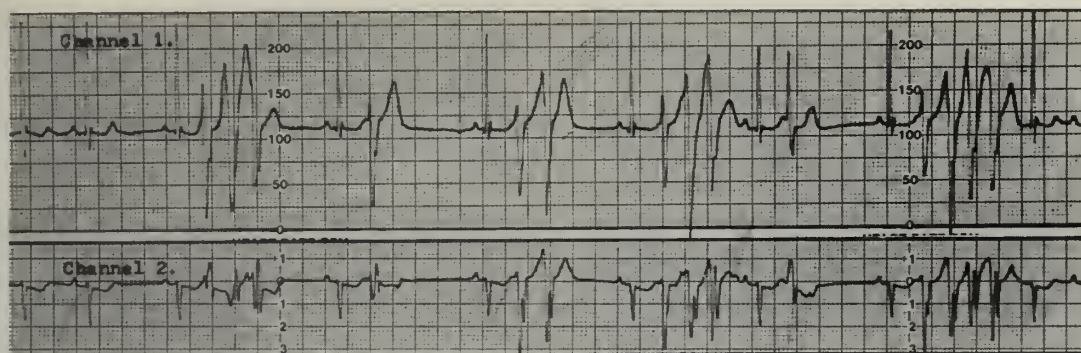


Figure 3. Holter ECG. Salvos of VPB's, VT and AV dissociation were observed.

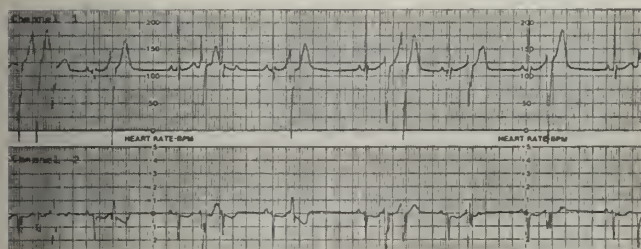


Figure 4. Holter ECG. Coupling intervals varied, and the morphology of the last beat differed; possibly it induces retrograde atrial depolarization. The fifth VPB may be interpolated.

singular (some interpolated with retrograde concealed conduction), coupled, multifocal, R-on-T and noncoupled ventricular ectopy or ventricular premature beats (VPB's). The coupling intervals varied, but were not typical for parasystole.

Discussion

VT has been observed relatively rarely in pediatric subjects, especially if only primary VT is considered. By 1985, only 107 children and adolescents with idiopathic recurrent VT (without structural heart disease or systemic disorders) had been reported. However, VT is the second most common type of tachycardia in children, supraventricular tachycardias being more commonly encountered.^{3-8, 11-19} VT may be associated with a normal heart, or with structural heart disease; the presence of the latter represents a most significant risk factor.^{4, 13, 20-22}

The etiologies of VT in pediatric practice are numerous, as seen in Table I.^{2-8, 13, 18-26}

A wide range of electrocardiographic patterns have been included in the broad VT panorama. Repetitive VT (RVT) is a distinct syndrome of classical VT, and may have been first described by Sir Thomas Lewis in 1909 under the title of "single and successive extrasystoles".¹⁰ It is an extrasystolic VT, designated "extrasystolie a paroxysmes tachycardiques de Gallavardin",⁹ "tachycardia en salvos",^{27, 28} "repetitive paroxysmal tachycardia of Parkinson and Papp"²⁹ and "repetitive monomorphic VT". It is characteristically incessant while demonstrating repetitive runs of ectopic beats numbering from 1 - 12, usually 4 - 5 beats, in recurrent

Table I

Etiologies of Ventricular Tachycardia in Infants and Children

Viral myocarditis. Rheumatic myocarditis.
Upper respiratory infections. Diphtheria.
Cardiomyopathy.
Congenital heart disease. Postoperative tetralogy of Fallot;
Ventricular septal defect.
Cardiac tumors.
Mitral valve prolapse.
Sick Sinus Syndrome.
Prolonged Q-T Interval syndromes (Jervell-Lang-Nielsen,
Romano-Ward).
Metabolic, hypoxemic and electrolyte disorders.
Surgery of the heart and cardiac catheterization.
Aortic valve disease.
Arrhythmogenic right ventricular dysplasia (Fontaine's Disease).
Anesthesia and drug toxicities.
Skull fractures.
Emotional disturbances and stress.
Hyperadrenergic states; catecholamines; exercise. Cardiac neural lesions.
Congenital anomalies of the conduction system.
Fibrosis and fat infiltration in the myocardium and conduction tissues.
Accelerated idioventricular rhythm.
Familial
Idiopathic

paroxysms, separated by a few sinus conducted beats between the paroxysms. In idiopathic VT the rate varies from 130 to 300 beats per minute. There may be a monomorphic or two distinct QRS morphologies. Variations in conduction of impulses may explain the different QRS contours. A left bundle branch block morphology is characteristic and denotes origin from the right ventricle. The initiating beat of a salvo may show a distinct contour and coupling interval from the subsequent beats. Ventricular fusion beats and atrioventricular dissociation are observed, supporting the diagnosis of VT. Post-paroxysmal pauses may follow retrograde atrial conduction. Isolated VPBs with the same morphology as that of the VT, bigeminy, sustained tachycardia and intermediate forms may be observed, as well as reciprocal beats. Repetitive patterns of paroxysms are characteristic. The Q-T interval may differ. The VT may occur or disappear with exercise.^{3, 8-10, 12, 19-21, 24, 27-35}

Reentry, parasystole, increased automaticity, triggered activity and delayed after-potentials have all been invoked as underlying electrophysiological mechanisms in these tachycardias. Their origins have been found in

the right ventricular outflow tract, the right ventricle, the septum and left ventricle, but predominantly in the right ventricle.^{2, 3, 10, 30-36}

Primary IRPVT in children, often associated with none or minimal structural heart disease but being observed in the healthy young, has had a reputation of benignity, well-tolerance and a good prognosis (only 6 deaths and 8% mortality by 1984 - all treated with antiarrhythmic drugs; 9 deaths, 2 asymptomatic; no deaths in 26 patients; and 7% mortality in four recent reviews). It may even disappear spontaneously.^{4, 6-9, 11-13, 18, 20, 23, 27, 28, 30, 35, 37}

However, these patients may have symptoms and complications, such as dizziness, dyspnea, fatigability, palpitations, congestive heart failure, syncope, seizures, cardiac arrest and even rarely sudden death, especially in patients with structural heart disease.^{2, 7, 10, 13, 18, 21-23, 34, 38} Prior VT was present in 1% of a series of sudden death pediatric patients.² Rowland and Schweiger^{34, 39} reported a death in a child with repetitive paroxysmal VT; death occurred in 3 of 29 cases in Cass' series;⁴⁰ in 2 of 4 cases reported by Stock;¹⁰ 3 of 24 cases of idiopathic VT died suddenly.⁸ Garson² found postoperative patients with congenital heart disease involving ventriculotomy, especially cases of tetralogy of Fallot, and with postoperative aortic valve disease, and cases of congestive cardiomyopathy, to reflect high-risk groups. Up to 13% deaths in 8 years have been reported in untreated patients with idiopathic VT.⁸

Conflicting criteria regarding therapy have been proposed. Moreover, these patients tend to be resistant to antiarrhythmic therapy. Antiarrhythmic therapy has been recommended for symptomatic patients. For the asymptomatic patient the course of action is less clear; opinions differ. Perhaps, no treatment is indicated if the heart is normal, if the rate of the VT is slow and if the tachycardia is self-terminating.^{2, 4, 7, 8, 13, 18, 30, 34, 39}

Antiarrhythmic therapy, such as phenytoin and mexiletine, has been generally recommended if the heart was abnormal. Digoxin, beta-blockers, type I agents, encainide, lidocaine and amiodarone have also demonstrated some antiarrhythmic effect.^{1-4, 13, 16, 35} Garson² found phenytoin, mexiletine, tocainide and propranolol to be particularly effective, and quinidine to be less effective, in postoperative patients. He has chosen to treat postoperative tetralogy of Fallot patients showing tachycardia on an ECG, and VPBs, couplets or VT on a Holter study. Such therapy resulted in disappearance of symptoms, and usually 100% suppression of ventricular arrhythmias by Holter monitoring. Other series of idiopathic recurrent VT have enjoyed less than complete success in control of symptoms and arrhythmias.³⁹ DC shock therapy has also been applied.⁴¹ Cardiac surgery for heart tumors, right ventricular dysplasia, and for postoperative VT's such as those complicating repair of tetralogy of Fallot, may achieve success.^{1-4, 13, 24, 26, 37, 42}

Holter monitoring, two-dimensional echocardiography, treadmill exercise testing, magnetic resonance imaging, serological testing for viruses, endomyocardial biopsy, cardiac catheterization with angiography and electrophysiological studies (EPS) have been recommended for evaluation of pediatric patients with VT. The role of EPS is somewhat controversial, but may be

indicated if the VT is not controlled by drugs, if the VT is idiopathic, if the patient is symptomatic and if the tachycardia is exercise-related. However, programmed electrical stimulation may or may not induce RVT. More often than not, idiopathic VT is inducible.^{3, 8, 13, 20, 31-34, 37, 39, 43, 44}

Resumen: Este artículo describe un episodio de taquicardia ventricular repetitiva en un joven de seis años de edad, que le causó a la muerte luego de un curso de palpitaciones sintomáticas, convulsiones tónicas, pérdida de conocimiento, arresto cardiopulmonar y fibrilación ventricular. Se revisa la literatura de taquicardia ventricular en la práctica pediátrica, enfatizando la muy baja mortalidad de la variante de taquicardia ventricular idiopática paroxismica repetitiva.

Acknowledgement

To Dr. José Ramón Gómez, Pediatric Cardiology Section, San Juan City Hospital, Río Piedras, Puerto Rico.

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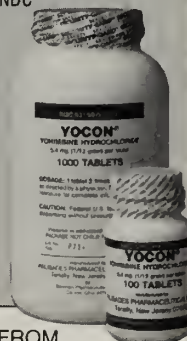
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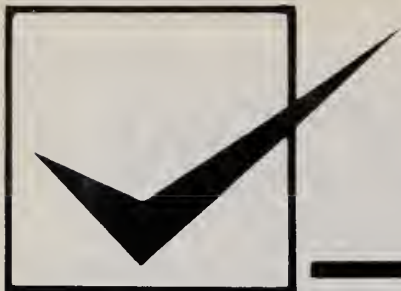
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Robert G. Struble, PhD
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Abstract: Understanding the causation of degenerative changes is central to modern hypotheses concerning the etiology of Alzheimer's disease (AD). Ever since the original descriptions by Blocq, Marinesco, Redlich and Alzheimer, speculative models of the characteristic pathology of AD (mostly senile plaques) have been proposed. These models were based on analyses of senile plaque constituents, the topography of pathology, relationship to clinical symptomatology and cytoskeletal disruption such as neurofibrillary tangles and granulovacuolar degeneration. Some of the hypotheses entertained at the turn of the century, including the infectious origin of senile plaques, a breakdown of the blood-brain barrier (dysoria), and the evolution of plaques, are currently being pursued, misquoted and sometimes "rediscovered". Understanding some of the early thoughts and discoveries not only provides scientists with well deserved recognition but also suggest ideas amenable to experimentation.

"...it speaks for itself that further research into the pathology of insanity would aid in the treatment and prevention of the insane"

*Annual Report of the Asylums Committee
Brit Med J 549: 1984.*

In 1902, Russell reported that the number of elderly patients being hospitalized was increasing yearly.¹ At the time of his writing, they accounted for one-fourth of all hospital admissions.¹ Furthermore, at least two-thirds of all patients over 60 years of age admitted to asylums were diagnosed as having senile dementia.² Recognition of an increasing population of elderly

demented persons combined with the introduction of the Bielschowsky silver impregnation method to produce numerous neuropathological discoveries upon which our present knowledge of senile dementia is based. In this article we present some of the research, ideas, and discoveries of these early investigators.

Early History (500 B.C. - 1892)

The vulnerability of aged individuals to a variety of mental disorders has been long recognized. One of the earliest records in this regard appeared around 500 B.C. when Solon modified the making of wills to exclude those persons with impaired judgement due to old age.³ Unfortunately, the recognition that this cognitive decline was not a necessary concomitant to aging had to wait until society viewed the practice of autopsies as acceptable and until medicine classified senile dementia as a clinical entity.

In the early 1800's mental disorders were attributed to diseases of the mind without a structural substrate.⁴ Dementia was grouped with other insanities (e.g.: moral madness, incoherence, monomania and mania)⁵ and characterized as a disease seen in persons over 60 years of age, having trouble with ambulation, "weakness of intellect" and diminution of memory.⁶ Dementia was occasionally reported in young⁷ persons usually progressing to abrogate all mental faculties.⁶ Several different etiologies were known to cause clinical deterioration similar to that observed in dementia, most notably apoplexy (including lacunes), tumors, scars, hemorrhages, protracted mania, epilepsy and fevers attended with severe delirium.^{5, 6} Lesions, when found in the basal ganglia, cerebellum or white matter, were thought to underly the motor deficits seen in dementia.⁶ Intellectual impairment was associated with gray matter abnormalities including gyral atrophy and degeneration of neurons and vessels.⁶ This pigmentary or fuscous degeneration of neurons (i.e.: lipofuscin) consisted of accumulation within vacuoles of a golden-yellow substance which turned black in osmic acid specimens and was associated in advanced cases of dementia to cell death.

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Although the quest for a pathological correlate of dementia was still an important issue in the late 1800's, the paucity of neuropathological findings led many researchers to entertain other questions. Could there be "loci" in the brain that determined intellectual function? What was the cause of the pathological changes thus far described in dementia?

In an early study of cytoarchitecture and dementia involving over 200 patients, Bolton noted wasting of the prefrontal region as the most salient feature of mentally deficient subjects.¹⁰ He concluded that this area was responsible for man's intellectual functions, and dementia reflected atrophy due to insufficient durability of the outer cell layers of the cortex. In the terminology of Gowers, this type of changes was called an "abiotrophy" and implied a passive process with progressive failure of the vital energy of a tissue.¹¹ In contrast, other authorities maintained that derangement in function of various organs gave rise to a chronic auto-intoxication of cells¹² resulting in neuronal cell loss and senile involution.

Senile Plaques (1892-1911)

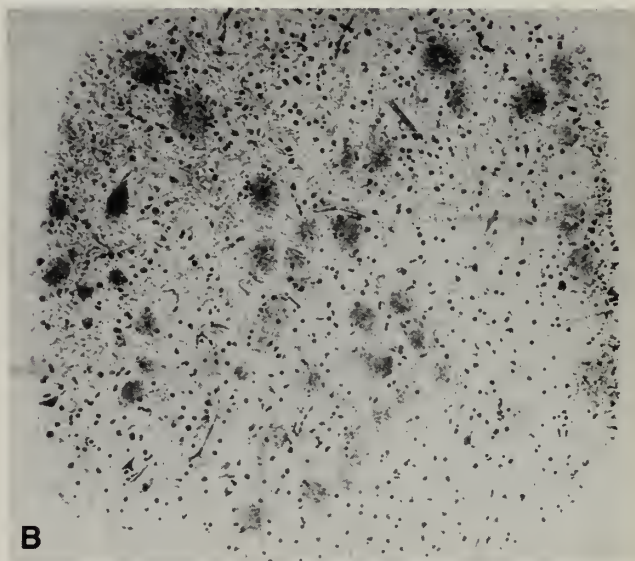
The earliest description of a senile plaque is often attributed to Blocq and Marinesco (1892).¹³ In a report on the neuropathological findings of nine elderly patients having "essential" epilepsy, these authors noted five cases exhibiting multiple round lesions which they called "nodules de sclerose neuroglie", emphasizing the presumed glial nature of these nodules. Blocq and Marinesco believed that their findings were similar to those of other French authors, most notably P. Chaslin.¹⁴ The latter author described a network of neuroglial fibrils forming cone-shaped structures in abnormal brain gyri of three epileptic patients. The illustration of this lesions in Chaslin's article, however, does not resemble senile plaques.

In 1898, Dr. Emil Redlich provided the first unequivocal description of senile plaques (Figure 1 a, b) in age individuals.¹⁵ His plaque, or foci of "miliary sclerosis", were circular areas with a homogenous or fine granular material in the center, surrounded by a layer of glial fibers and cells. Redlich thought that these lesions were the results of neuronal degeneration and concomitant glial proliferation. A similar point of view was later expressed by Bonfiglio and Perusini.^{16, 17}

In the same year (1898) that Redlich described miliary sclerosis, Alzheimer made his first major contribution to the pathology of dementia by describing cerebrovascular colloid hyalinization of blood vessel walls resembling congophilic angiopathy.¹⁸ In 1904, he described plaques as composed of glial fibers surrounding a substance similar to corpora amylacea.¹⁹ However, Alzheimer's most notable contribution occurred in 1906, at a meeting of the Southwest German Society of Alienists in Tübingen, where he described the case of a notably young (51-year-old) woman who presented with jealousy, "weakening of mental faculties" and died four and a half years after onset of her disease process.²⁰ The autopsy disclosed a diffusely atrophied brain with numerous foci of "miliary sclerosis" and a striking alteration of neuro-



A



B

Figure 1. (A) Dr. Emil Redlich was the first person to describe plaques in senile dementia. Portrait courtesy of the National Library of Medicine. (B) Plaques or foci of "miliary sclerosis".

fibrils. Patients with a similar clinical history were soon denoted as having Alzheimer's disease (AD), a term first introduced by Kraepelin, his mentor, in 1908.²¹ Both Alzheimer and Bielschowsky believed that plaques were the product of deposition in the cortex of an undetermined chemical substance ("Aufbau Produkte") derived from an abnormal metabolism of various nervous elements.^{20, 22}

After extensive studies, Fischer (1907-1908) concluded that plaques were characteristic of dementia.^{23, 24} Other authors differed with this observation, since similar lesion were found at autopsy in persons without dementia in cases of gastric carcinoma,²⁵ tabes,¹⁷ a normal aged individual,²⁶ and many other conditions.²⁷⁻²⁸ Perusini even reported their presence in the brain of a guinea pig.¹⁷

Fischer described plaques as being foci of necrosis with homogenous centers surrounded by glial fibers and club-shaped processes composed of proliferated or thickened axis cylinders (Figure 2).^{23, 24} The term "Drussy necrosis" was applied to the lesion due to similarity between plaques and Drusen (not Drüsen which means gland), the agglomeration of spores and filaments of actinomyces. Fischer argued, for the first time, in favor of a possible infectious origin of the plaque.

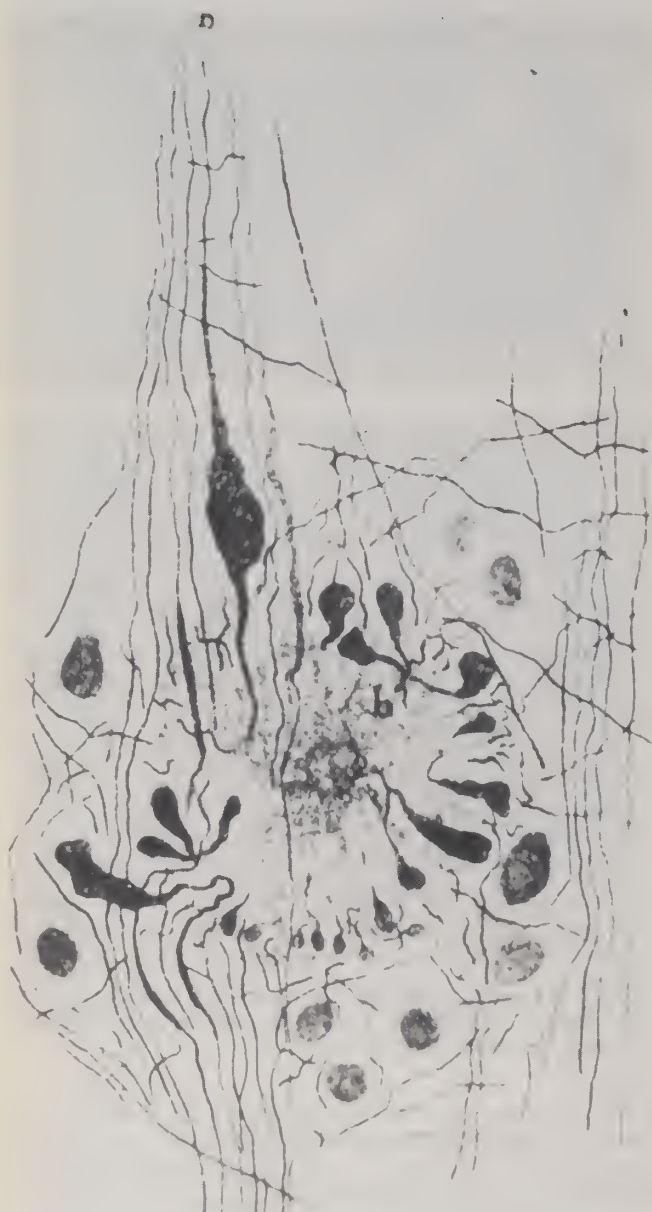


Figure 2. Fischer described plaques as being foci of necrosis or degeneration with homogenous centers. Glial fibers and some club-shaped processes composed of proliferated or thickened axis cylinders were visualized at the periphery.

In 1911, Barret proposed that plaques shrink as they evolve.³⁰ He also argued that the localization of plaques corresponded to clinical manifestations exhibited by demented persons. Other authors described relationships among plaques and atherosclerosis, brain weight, and atrophy. Conversely, Oppenheim (1909) found no relation between atherosclerosis and plaques.²⁵ In a study of 26 brains of senile psychosis, Sigg concluded that arteriosclerotic brains from patients up to 63 years of age do not show plaques.³¹ Southard, in his series, found no association between brain weight, atrophy, and dementia.³² Fuller (1911) found no correlation between brain weight or atrophy and the presence of miliary structures while noting that plaques were found in greatest numbers in the frontal lobe and hippocampus, less frequently in the basal ganglia and medulla, and never in the spinal cord.²⁶

Simchowicz (1911) introduced the term senile plaques for the first time when he reported the pathological findings in the brain of 108 elderly patients.³³ Senile plaques were quantitated in order to differentiate dementia from other conditions:

"The mere presence of senile plaques does not necessarily indicate senile dementia. The number, arrangement, and size of plaques should be taken into consideration. The most important is the number. Four or five plaques (Leitz, obj 3, 0e 3, magnification 80) in one optic field can be found in the normal senium. However, while the normal old person of ninety-four years of age presents six plaques in the frontal region the senile dementia of seventy-two years of age shows 52 in the same region... Not only the number but the arrangement of the plaques is of importance. In normal aging and in psychoses other than senile dementia, the plaques are more or less scattered, while in senile dementia they tend to show grouping. In addition to this, the size of the plaques can be of differential diagnostic value. In senile subjects without psychoses, small sized plaques are encountered, while in the senile dementia one observes a giant form among the smaller and medium sized ones. The giant form is never observed in any psychosis except senile dementia."³³

Soon after senile plaques were described, new questions arose about the relationship between dementia, plaques, and other pathological features of AD. Simchowicz in his series was interested in those patients that presented with dementia but showed no plaques.³³ Schnitzler reported a case with neurofibrillary degeneration but no plaques, while on the contrary, Alzheimer described a case in which plaques were present, but no neurofibrillary tangles were evident.^{34, 35}

Origin of Amyloid in Plaques

The term amyloid was introduced into the medical literature by Virchow in 1851 to describe a "lardaceous" substance which reacted with iodine and sulfuric acid to give a red or violet color.³⁶ Amyloid bodies or similar substances were identified by Alzheimer as forming part of the "miliary sclerosis" (i.e.: plaques) described by

Redlich.¹⁹ Alzheimer believed that these lesions were the result of abnormal metabolism of neuronal elements. The chemistry of this substance was initially regarded as calcium amyloid by Ziveri³⁷ or a monophosphatide by Marinesco and Minea.³⁷ The amyloid content of senile plaques was first clearly recognized by Divry but soon afterwards, other researchers could not confirm its presence in all senile plaques.^{38, 39} This observation, that not all senile plaques contained amyloid, led von Braunnmuhl and Marinesco to explain the formation of senile plaques by a process of aging colloids within the central nervous system.^{39, 40} A different hypothesis arose from the description of perivascular stellate plaques in 1910 by Fischer and the early finding of granules within vessel walls resembling the amyloid core of plaque.⁴² These observations led several authors to postulate a dysoric (dys-abnormal, oro-border or barrier) hypothesis for AD.^{25, 29, 41-44} At present, the origin of amyloid in plaques is still unknown.

Other Neuropathology Changes

In the early 1900's most of the research in Alzheimer's disease concerned senile plaques, however, many other important neuropathological observations had been made. Mills and Schively (1897) described the microscopic findings in the brain of a 64-year-old demented woman.⁴⁵ The silver phosphomolybdate method of Berkley was used to examine individual cells. Pyramidal neurons were most prominently affected, exhibiting distortion of the cell soma, loss of "gemmulae" and moniliform swellings or clubbed extremities of dendrites. In some cases, the basilar dendrites were lost and the apical branch roughened and deformed in contour. These abnormalities could account for the cytoarchitectural dysruption and rarefactions of the neuropil reported in dementia by Sarteschi (1909).⁴⁶

Using the Bielschowsky silver impregnation method, Alzheimer first described alterations of neurofibrils in the brain of a demented women.²⁰ This change initially affected few fibrils but progressed to form thick aggregates. Finally, the nucleus and cell desintegrated and only a tangled bundle of fibrils remained to indicate the site of a former neuron. Less impressive thickening of neurofibrils and aggregates had been previously reported by Donaggio in experimental animals subjected to the environmental stresses of cold and inanition, and after acute poisoning with picrotoxin, strychnine or chloral hydrate.⁴⁷ Cajal, Tello and Marinesco used the term hypertrophy of neuroifibrils to describe neuronal changes in animals during hibernation and after injection of the rabies virus.⁴⁷⁻⁵⁰

Although the initial observation of granulovacuolar degeneration is often attributed to Simchowicz, neurons with fine canals having cavernous dilations containing a small round body were described in 1904 by Cajal.⁴⁹ In rabies, Nelis named the spatial arrangement of granulovacuolar changes "état spirematerux" and Tello reported its occurrence in lower vertebrates during hibernation.^{47, 48} In 1911, Simchowicz was the first person to describe these changes in dementia.³⁴

In conclusion, the importance of neuropathological

changes in AD is emphasized by recent studies correlating their numbers with the severity of dementia. This fact has led some authors to quantify plaques or tangles to establish the diagnosis of AD and to use immunocytochemical and electron microscopic methods to elucidate their components. The information gained from such studies has led modern investigators to postulate different origins for the neuropathologic changes in AD, including infectious agents, break-down of the blood brain barrier (dysoria), and degeneration of axons and other cortical elements. However, these ideas are not new and as we have seen, they have roots at the beginning of this century. In 1911, Simchowicz first drew attention to the diagnostic significance of senile plaques, Fischer (1907) claimed their infectious origin, and many others correctly identified the basic components of senile plaques.

Recognition of these early thoughts and discoveries not only provides investigators well-deserved recognition but also suggests ideas amenable to experimentation. Thus, Barret's suggestions in 1911 that clinical symptomatology in AD may be related to distribution of senile plaques, the possible morphological evolution of senile plaques, the suggestion by many authors of a dysoric process in AD and the cytoarchitectural disruption of neurons observed under various experimental conditions are still worth pursuing.

Resumen: Las investigaciones acerca del origen de cambios degenerativos en la enfermedad de Alzheimer (AD) han dado lugar a un innumerables de especulaciones en cuanto a su posible etiología. Partiendo de las descripciones originales de Blocq, Marinesco, Redlich y Alzheimer, modelos especulativos basados en la patología característica de AD (mayormente placas seniles) han sido propuestos. Estos modelos se han basado en el análisis de los constituyentes de placas seniles, cambios neurofibrilares y degeneración granulovacuolar, la topografía de los cambios patológicos y su relación a las manifestaciones clínicas. Algunas de la hipótesis del principios del siglo, incluyendo el origen infeccioso de las placas seniles, el rompimiento de la barrera hematoencefálica, y la evolución de las placas seniles, son investigadas al presente, algunas veces tomadas fuera de contexto y en ocasiones redescubiertas. El entendimiento de estas primeras ideas y descubrimientos provee el necesario reconocimiento a los primeros investigadores al mismo tiempo que proporciona ideas para futuras investigaciones.

Acknowledgement

This paper has benefitted from discussions with Drs. Janice Stevens, Arthur Clark and Linda Cork. Ms. Teresa Tolbert provided the secretarial assistance.

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MEDICAL ASPECTS OF NUTRITION

Vitamin Preparations as Dietary Supplements and as Therapeutic Agents*

Vitamin preparations are used extensively in the practice of medicine and are valuable when used properly. It is important that a clear distinction be made between vitamins as dietary supplements and vitamins as therapeutic agents. It is also important for the practitioner to understand the usefulness and the limitations of given vitamin preparations in given clinical situations.

DEFINITIONS

Recommended Dietary Allowances (RDA)

The RDA are "the levels of intake of essential nutrients considered, in the judgment of the Committee on Dietary Allowances of the Food and Nutrition Board on the basis of available scientific knowledge, to be adequate to meet the known nutritional needs of practically all healthy persons."¹ (The abbreviation RDA is used for both the singular and plural of the term in accordance with National Academy of Sciences' usage.¹) The RDA are not requirements for an individual, but recommendations for the daily amounts of nutrients that *populations* should consume over a period of time to protect all members of that population. With exception of the allowances for energy, RDA are estimated to exceed the requirements of most individuals to ensure that the needs of nearly all members of a population will be met. In this country, RDA are set approximately two standard deviations (SDs) above the mean requirement and will therefore encompass the needs of 97% of the population. Allowances are established for a wide range of age, weight and sex groups and for pregnancy and lactation.

The RDA have not been set for all recognized essential nutrients. In the ninth edition of *Recommended Dietary Allowances*, issued in 1980,¹ RDA were set for only 10 of the 13 known vitamins. Because of the lack of information on which to base allowances, the RDA committee established ranges of Estimated Safe and Adequate Daily Dietary Intakes for vitamin K, pantothenic acid and biotin.

Since the RDA are established for healthy people, they do not cover special needs for nutrients by persons with specific clinical problems, such as premature birth, inherited metabolic disorders, infections, catabolic states including weight reduction, chronic diseases and drug therapy, all of which may alter requirements for given vitamins.

U.S. Recommended Daily Allowances (U.S. RDA)

These standards were developed by the Food and Drug Administration (FDA) for use in the nutrition labeling of the general food supply and for labeling dietary supplements and special dietary foods.² They are based mainly on the 1968 RDA. For practical purposes, the U.S. RDA use only four population groups (compared with 26 groups listed in the 1968 and 17 on the 1980 RDA editions).

Generally, the highest values for the ages combined in a U.S. RDA were used. For example, the U.S. RDA for the population group incorporating adults and children over four years of age are representative, generally, of the RDA recommended for a teenage boy. The U.S. RDA also include estimates for allowances of biotin and pantothenic acid. The U.S. RDA for vitamins are shown in Table 1.

Table 1—U.S. Recommended Daily Allowances (U.S. RDA) for Vitamins²

Vitamins	Infants	Children Age 1 to 4 y	Adults and Children Age ≥4 y	Pregnant or Lactating Women
Vitamin A, IU	1500	2500	5000	8000
Vitamin D, IU	400	400	400	400
Vitamin E, IU	5.0	10	30	30
Ascorbic acid (vitamin C), mg	35	40	60	60
Folic acid, mg	0.1	0.2	0.4	0.8
Thiamin, mg	0.5	0.7	1.5	1.7
Riboflavin, mg	0.6	0.8	1.7	2.0
Niacin, mg	8.0	9.0	20	20
Vitamin B ₆ , mg	0.4	0.7	2.0	2.5
Vitamin B ₁₂ , µg	2.0	3.0	6.0	8.0
Biotin, mg	0.05	0.15	0.3	0.3
Pantothenic acid, mg	3.0	5.0	10	10

Adequate Diet

A nutritionally adequate diet is composed of foods that meet an individual's vitamin and other nutrient requirements and meet but do not exceed his or her energy requirement. Nutritional adequacy is best ensured through the use of a wide variety of foods³... The current

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Council on Scientific Affairs American Medical Association, 535 N. Dearborn Street, Chicago, IL 60610

guide⁴ developed by the U.S. Department of Agriculture allows people to plan adequate diets by selecting foods rather than calculating nutrients.

Commonly eaten foods are divided into five groups on the basis of similarity in composition and nutritive value⁴ ...fruit/vegetable, bread/cereal, milk/cheese, meat/poultry/fish/beans, fats/sweets/alcohol... Adhering literally to the minimum number and size of servings recommended provides about 1200 kcal (504kJ), adequate protein and most of the vitamins and minerals needed daily.⁴ Individuals can increase their nutrient and total energy intake by consuming larger portions and more servings and by selecting food from the fifth food group. If the total energy intake falls below 1200 kcal (5040kJ), it becomes increasingly difficult to obtain all of the protective nutrients in adequate amounts and supplements may be needed.

Dietary Guidelines for Americans,⁵ issued by the U.S. Department of Agriculture and Health and Human Services, also recommends eating a variety of foods from the major food groups to obtain a "well-balanced diet"; the guidelines do not specify the number and size of servings.

Vitamins as Dietary Supplements

A vitamin preparation used as a dietary supplement is one designed to increase the dietary intake of one or more essential vitamins. Such preparations ordinarily contain given vitamins in amounts of 50% to 150% of the U.S. RDA.

Healthy adult men and healthy adult nonpregnant, nonlactating women consuming a usual, varied diet do not need vitamin supplements. Infants may need dietary supplements at given times, as may pregnant and lactating women. Occasionally, vitamin supplements may be useful for people with unusual lifestyles or modified diets, including certain weight reduction regimens and strict vegetarian diets (i.e., one that excludes all foods of animal origin).

Infants and Children

The normal breast-fed infant of a wellnourished mother receives sufficient quantities of all vitamins except vitamins K and D. Concerning vitamin K, newborns have sterile intestines and cannot initially synthesize menaquinones. Since human milk contains [minimal] phyloquinone (vitamin K₁)⁶... it is recommended that all newborns receive a single intramuscular dose of 0.5 to 1.0 mg of phyloquinone as prophylaxis against hemorrhagic disease of the newborn. Low birth-weight infants may require a second injection at about one week of age. Because the vitamin D content of human milk is extremely low (about 22 IU/L), breast-fed infants may need supplemental vitamin D (400 IU/d) if they have limited exposure to sunlight.⁷ Breast-fed infants whose mothers are strict vegetarians require supplemental vitamin B₁₂.⁷

The Infant Formula Act of 1980 mandates adequate levels of vitamins and other nutrients in commercial infant formulas. Home-prepared evaporated milk or pasteurized cow's milk formulas should be supplemented

with vitamins C and D.⁷

By the time the infant reaches one year of age, the diet should be composed of a variety of foods. A convenient guide to foods is the revised food guide⁴ or any similar set of guidelines⁵ to promote variety in the diet. Application of sound dietary practices should eliminate any need for supplemental vitamins after infancy in essentially all healthy children.

Adults

Healthy adults, 18 years of age and older, receiving adequate diets should have no need for supplementary vitamins. Dietary practices in the United States, however, have changed in ways that may have reduced the overall vitamin delivery from the diet.⁸ Since the turn of the century, consumption of processed foods has increased, many more meals are eaten away from home and a greater portion of the diet is consumed as between-meal snacks. In some instances, poverty may limit the amount and quality of foods consumed, which may necessitate supplemental vitamins. Before deciding whether a vitamin supplement should be recommended to an adult, however, a history regarding the adequacy of dietary intake, usual dietary practices and specific issues of life-style and life situation must be carefully evaluated. If the individual appears not to be meeting his or her recommended intake of vitamins in the diet, an attempt to correct the situation by improving the selection of foods and the pattern of eating should be made.

As regards the elderly, neither the Food and Nutrition Board of the National Academy of Sciences/National Research Council¹ nor the World Health Organization⁹ recognizes any need for increasing the vitamin and mineral allowances for healthy elderly individuals above those recommended for healthy young adults. In fact, the Food and Nutrition Board¹ recommends a slightly decreased daily allowance for men over the age of 51 years for niacin, riboflavin and thiamin. This reduction is related to an overall decrease in energy exchange by the elderly, particularly elderly men.

Although requirements for vitamins are not increased by age, socioeconomic conditions and reduced physical activity among the aged may lead to a curtailment in total food intake. Under such restriction, the use of a vitamin preparation in the prevention of deficiency may be indicated. When such is the case, the dose of vitamins (50% to 150% of the U.S. RDA) recommended elsewhere in this report as effective in the prevention and treatment of specific deficiency states or multiple-deficiency states in most adults are adequate for use in the elderly population.

A specific instance in which supplemental vitamins are very often indicated is for the pregnant or lactating woman. The physiologic demand for vitamins during pregnancy over and above the normal requirements are shown in Table 1. Even though appetite and dietary recommendations for pregnant and lactating women encourage a greater intake of food, the recommended increases in vitamin intake above basal requirements may not be achieved. For this reason, vitamin supplements are often prescribed for pregnant and lactating women. Surveys among less privileged segments of the U.S. population

reveal deficits in vitamin intakes relative to requirements during pregnancy and lactation.¹⁰

Vegetarianism has provoked concern about vitamin adequacy, particularly for strict vegetarian diets (these diets exclude all foods of animal origin). Vitamins B₁₂, D and riboflavin may be deficient in diets of strict vegetarian (vegans) infants and children. Intake of these vitamins will be adequate if appropriately fortified soy formula or fortified soybean milk drink is used.¹¹ Adequate vitamin B₁₂ can be a problem for adult vegans. Adequate intake can be provided by supplementation of the diet with vitamin B₁₂. Inadequate vitamin intake is not a problem for persons who consume lactovegetarian diets (these diets include milk or milk products) or lacto-ovo-vegetarian diets (these diets include dairy products and eggs).

Certain weight-reduction diets may lead to inadequate vitamin intakes.¹² Even with a sound approach to slimming, it may be difficult to meet recommended vitamin intakes at an energy level of 800 to 1000 kcal/d (3360 to 4200 kJ/d) and hence a modest supplement may be recommended. The addition of a supplemental vitamin preparation to a very low-energy weight reduction program, however, will not necessarily make the diet safe. The overall metabolic status of persons consuming a low-energy diet should be periodically evaluated by a physician.

Emotional disturbances can also alter dietary patterns and energy intake. Depression is associated with a variety of eating disturbances. Patients with anorexia nervosa and the binge-purge syndrome (bulimia) usually have very low net energy intakes. Vitamin intakes may be insufficient but, once again, the clinical situation requires a more comprehensive analysis and solution than the addition of a vitamin supplement to an otherwise insufficient diet.

Vitamins as Therapeutic Agents

The vitamin preparations used for the treatment of deficiency diseases or other pathologic conditions should be clearly labeled for that purpose. They should not be used as dietary supplements. They should be recommended by physicians according to specific medical indications. The amounts of each vitamin in such vitamin preparations should not exceed two to the times the RDA, depending on the vitamin.

Vitamins in therapeutic amounts are indicated only for the treatment of deficiency states or pathologic conditions in which absorption and utilization of vitamins are reduced or requirements increased and for certain nonnutritional disease processes... The decision to employ vitamin preparations in therapeutic amounts clearly rests with the physician and the importance of medical supervision when such amounts are administered is emphasized. Therapeutic vitamin mixtures should be so labeled and should not be used as dietary supplements.

The quantities of vitamins included in mixtures intended for therapeutic use should not exceed two to ten times the U.S. RDA, depending on the vitamin. Vitamins, like all biologically active substances, may cause qualitatively different responses at different dose levels.

When a vitamin is recommended in the therapeutic range, the dose will vary for different indications... The following conditions justify the use of therapeutic vitamins: deficiency diseases..., malabsorption..., prolonged illness..., enteral and parenteral nutrition..., alcoholism... burns..., renal failure and dialysis..., vitamin-nutrient and drug-vitamin interactions..., genetic diseases...

Misuses of Vitamins

The FDA has estimated that 40% of the adult population uses vitamin and mineral supplements on a daily basis¹³... With such widespread use of vitamins by the American public, there is ample opportunity for misuse. Misuse of vitamins is considered any application of a vitamin or vitamins in a dose that is inappropriate or for a purpose that has no basis in established scientific practice. The rationales are often based on myths or distortions of experimental studies in laboratory animals. Some vitamins, such as A, E, C and B₆, are abused more commonly than others.¹⁴ Some persons have taken large doses of multivitamins in the belief that vitamins combat the chronic degenerative diseases or extend life. No objective benefits, however, have been demonstrated.

Some of the most frequently encountered examples of vitamin misuse include the following: vitamin E has been taken in large quantities in pursuit of rejuvenation, increased libido and improved sexual performance. Under the rubric of "orthomolecular psychiatry," large doses of niacin have been given for the treatment of a variety of mental disorders without measurable effect. Large doses of vitamin B₆ have been promoted for the treatment of carpal tunnel syndrome, premenstrual tension and mental disorders without established benefit.¹⁴ One of the most widely misused vitamins is ascorbic acid. There is no reliable evidence that large doses of ascorbic acid prevent colds or shorten their duration.¹⁵

Several vitamins have been heralded as anticancer agents, supposedly preventing the development of many types of malignancies. Although epidemiological studies have suggested that certain types of cancer are associated with a low intake of yellow and green vegetables and low plasma vitamin A levels, there is no evidence that taking large doses of vitamin A or carotene will prevent cancer in man.¹⁶ Vitamins with antioxidant properties, such as ascorbic acid and vitamin E, are often misused in an attempt to prevent cancer. Moreover, two randomized double-blind trials^{17, 18} demonstrated the failure of large doses of ascorbic acid to alter the rate of death in patients with terminal cancer.

Other substances claimed to be vitamins have been misused for both their supposed nutrient effects and therapeutic effects. No essential nutrients function has been reported for laetrile (wrongly referred to as vitamin B₁₇), pangamic acid (wrongly referred to as vitamin B₁₅) or the bioflavonoids, rutin and hesperidin (the so-called vitamin P factors). No evidence has been presented indicating that these substances are effective for any disorder. Choline, inositol and *p*-aminobenzoic acid have been listed as vitamins for some species in the past. They are not required by man and have no established vitamin function in man although they are nutrients and can be metabolized in the human body.

Toxic Effects of Vitamins

Undesirable effects ranging from trivial to major have been reported in association with use of inappropriately high doses of vitamins...

While an excessive dose of a vitamin is generally defined as 10 or more times the RDA, toxic effects from long-term daily ingestion of vitamin A have been reported with supplements ranging from five to 25 times the U.S. RDA.¹⁹ The specific toxic effects of fat-soluble and water-soluble vitamins are discussed below.

Fat-Soluble Vitamins

As a general rule, fat-soluble vitamins tend to cause toxic reactions at lower multiples of the RDA than do water-soluble vitamins. This is because fat-soluble vitamins tend to be stored in the body, rather than excreted, when ingested in excess. Some fat-soluble vitamins in excess of the concentration of the carrier proteins are taken up by membranes, with pathologic results.

The prolonged use of vitamin A in excessive doses can cause a variety of symptoms, including those related to skin and bone disorders, disturbed blood clotting with hemorrhage and other symptoms. In children, anorexia, pruritus and failure to gain weight are followed by irritability, bone pain and the limitation of joint motion. Larger doses of vitamin A, furthermore, are teratogenic.^{20, 21, 22}

Vitamin D is the most likely of all vitamins to cause overt toxic reactions in small multiples of the U.S. RDA. An epidemic of "idiopathic hypercalcemia" in infants, with anorexia, vomiting, hypertension, renal insufficiency and failure to thrive, occurred in England in the 1950s. It was traced to an intake of vitamin D between 2,000 and 3,000 IU/d.²³ In adults, dosages of 10,000 IU/d for several months have resulted in marked disturbances in calcium metabolism...

Relatively large amounts of vitamin E, in the range of 400 to 800 IU/d, have been taken for months to years without causing any apparent harm²⁴... The most significant toxic effect to vitamin E at dosages exceeding 1,000 IU/d is the antagonism to vitamin K action and the enhancement of the effect of oral coumarin anticoagulant drugs with overt hemorrhage.²⁵

Phylloquinone (vitamin K₁) has no reported toxic effects at 500 times its Estimated Safe and Adequate Daily Dietary Intake... [Menadione and its water-soluble derivatives] which require alkylation *in vivo* for vitamin K action should not be administered to patients as a source of vitamin K.

Water-Soluble Vitamins

Thiamin, riboflavin, vitamin B₁₂, pantothenic acid and biotin do not seem to cause toxic reactions in man when taken in large doses by mouth. On the other hand, niacin, vitamin B₆ and ascorbic acid are associated with well-documented toxicity syndromes.

Dosages of niacin (nicotinic acid) in excess of 5 g/d can cause severe flushing, itching, liver damage, skin disorders, gout, ulcers and impaired glucose tolerance.¹⁴

Recent evidence indicates that large dosages of vitamin B₆, in excess of 1.0 g/d over a period of months, can exert a direct toxic action on the peripheral nervous system.²⁶ Symptoms from this sensory neuropathy include unsteady gait and numbness of hands and feet.

Prolonged intake of ascorbic acid (vitamin C) in excess of 1.0 g/d may cause oxaluria, uricosuria and acidification of the urine. As a result, urinary stone formers appear to be at higher risk for calculi if they take large doses of ascorbic acid daily.²⁷ Ascorbic acid at these large doses can also produce false-positive results for glucose in urine and false-negative tests for blood in the stools, thereby confusing early detection of diabetes mellitus and gastrointestinal diseases, including cancer. In addition, excess ascorbic acid may produce diarrhea, alter the bacteriacidal activity of white blood cells and provoke "rebound scurvy" in adults who abruptly stop or reduce high long-term intakes. Rebound scurvy has also been reported in newborn infants of mothers who took large doses of ascorbic acid during pregnancy.¹⁴

Formulations of Vitamin Preparations Bioavailability

For a vitamin preparation to be effective, the vitamin ingredients must be bioavailable, i.e., they must be released in the intestine so as to be transported into the bloodstream for circulation to the tissues. There the biologically active form of the vitamin will achieve the desired metabolic effect. Bioavailability depends not only on the basic chemical characteristics of the vitamin but also on which ingredient form of the vitamin is administered and possibly on the physical form of the dosage. Bioavailability of vitamins and minerals may also be affected by the presence and amounts of other vitamins or minerals, e.g., the presence of ascorbic acid may enhance absorption of inorganic iron. On the other hand, zinc may precipitate folic acid and vice versa.

All products marketed as single ingredients or combination products should be in a form in which all active ingredients are biologically available. To ensure this, however, the current level of technology for determining the absorption of vitamins and minerals, singly or in combination, must be expanded. It is an important responsibility of the industry and the FDA to ensure that the necessary research is done to establish specific testing requirements for appropriate bioavailability of all active ingredients in vitamin products.

Rational Combinations

Restricted dietary intake, increased requirements as in pregnancy, or impaired absorption rarely affect a single nutrient. Thus, combinations of vitamins may often be the rational means of preventing or treating vitamin deficiencies. The following statement about vitamin combinations follows very closely the recommendations made in the monograph by the FDA's Expert Panel on Vitamin and Mineral Drug Products.²⁸

Multiple vitamin preparations that claim effectiveness for prevention or treatment of vitamin deficiencies should be formulated on the basis of supplying all those vitamins whose combined deficiencies may be expected in a signifi-

cant target population. When multiple deficiencies are present or are at increased risk of occurring, it would not be rational or safe to use preparations containing only two or three vitamins for the observed symptoms or deficiencies and thus unwittingly neglect therapy for other deficiencies. Therefore, a product containing only the fat-soluble vitamins is not recommended since the conditions of diet and intestinal disease that may predispose to depletion of some of these vitamins are more rationally treated with preparations that contain all needed fat-soluble and water-soluble vitamins (vitamin A, D, E and C, plus thiamin, riboflavin, niacin, pantothenate, vitamin B₆, folate and vitamin B₁₂). Vitamin K and biotin are not recommended in these products. Vitamin K deficiency rarely, if ever, occurs in this country because of dietary inadequacy, except in the newborn. Moreover, vitamin K could be hazardous for many patients receiving anticoagulant therapy. Biotin deficiency is virtually nonexistent in the U.S. population. Because the water-soluble vitamins (the B vitamins and vitamin C) are less well stored in the body than the fat-soluble vitamins and may be depleted more rapidly in the presence of altered intake or disease and because several B vitamins occur together in the same foods, a preparation containing all B vitamins with or without vitamin C to prevent or reverse disease in man is recommended.

These vitamins should be combined in amounts from 50% to 150% of the U.S. RDA for supplements to prevent nutritional disease and in amounts two ten times the U.S. RDA to treat disease... Where there is evidence that the combination of ingredients at certain levels may influence bioavailability of any other ingredient, careful testing is required.

Multivitamin formulations for total parenteral nutrition are described in a statement by the Nutrition Advisory Group of the American Medical Association.²⁹

Conclusions

This report makes specific recommendations about the use of vitamins as supplements and therapeutic agents.

Vitamins and vitamin mixtures, other than those discussed herein, may be demonstrated to be useful as dietary supplements or as therapeutic agents by further research. Until their value is established by convincing scientific evidence, however, such new preparations should not be advocated for general use.

Public health nutrition will be served best by the insistence on a scientifically sound basis for vitamin supplementation and therapy. All health practitioners should emphasize repeatedly that properly selected diets are the primary basis for good nutrition.

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IN MEMORIAM

Frederick Joaquín González, MD

Nació en Ponce el 17 de octubre de 1915. Vivió allí hasta los cuatro años y se trasladó a la ciudad de New York en el 1919, regresando a Puerto Rico en el 1947.

Cursa sus estudios de escuela superior en De Witt Clinton, New York desde el 1928 al 1932. Su educación universitaria la obtiene en el College of the City of New York desde el 1932 al 1934 y en el Saint John's University en Jamaica, Long Island desde el 1934 hasta el 1938.

Debido a limitados recursos económicos, desde muy temprano se ve obligado a trabajar para proveer sus propios medios y aprende a valorar la importancia que para su educación (meta principal) tenía el valor del dólar. Siempre demostró una gran capacidad para trabajar, persona honesta, con una convicción y motivación insaciable de crear, muy ordenado; ordenando siempre, pero también haciendo. Había que tener mucho cuidado con él cuando se trataba de argumentar sobre algún tema o decisión tomada en el pasado, no importa cuanto tiempo, pues tenía una "memoria de elefante" y podía uno encontrarse en dificultades.

Su educación médica la adquiere en la Universidad de Marquette en Milwaukee, Wisconsin del 1938 al 1942.

Antes de continuar con su trayectoria académica, quiero comentar un dato anecdótico que posiblemente pocos conocen: Freddy, desde temprano en sus años mozos desarrolló la habilidad de dirigir grupos. Tanto es así, que se convierte en Jefe de un grupo de jóvenes dominando el territorio donde ellos se movían. Al observar el éxito obtenido, se consideró apto para invadir el difícil y a veces productivo campo de los puños (el boxeo). Sus ilusiones no duraron mucho, pues tengo entendido que en una de sus primeras incursiones estuvo muy poco tiempo de pie. Como persona inteligente, esto fue suficiente para hacerle saber que este no era su campo.

Hace su internado en el Saint Vincent's Hospital de New York desde julio de 1942 a junio de 1943, convirtiéndose en el primer puertorriqueño en ser admitido a esa posición.

En el 1943 comienza una residencia en el Deaconess

Hospital de Milwaukee, Wisconsin y en ese mismo año es requerido por el "U.S. Navy" donde presta sus servicios hasta el 1946, siendo licenciado con el grado de "Lieutenant Commander". Participa con los llamados "P.T. Squadrons" y en Europa (Inglaterra) como oficial médico y anestesiólogo. Termina su entrenamiento en Anestesiología en el Bellevue Hospital y Polyclinic Hospital de New York del 1946 al 1947.



Al poco tiempo de terminar su especialidad regresa a Puerto Rico y se convierte en el primer anestesiólogo debidamente entrenado en llegar a la isla. El Hospital de Veteranos lo recluta para la posición de Jefe de Servicio de Anestesiología. Rápidamente se da a conocer y en muy poco tiempo se hace miembro de todas las Facultades Médicas de los hospitales de esa época. En vista de la necesidad tan grande

de servicios de anestesia, en el 1950 organiza una Escuela de Enfermeras Anestestistas de la cual han egresado más de 300 enfermeras anestestistas y en la actualidad, todavía está funcionando.

En el 1950 contrae nupcias con la Srta. Gloria Tancin, de cuyo matrimonio nacen dos hijos: Frederick Andrew, actualmente Obstetra-Ginecólogo, y Richard Steven, quien es Arquitecto.

Ese mismo año funda la Sociedad de Anestesiología de Puerto Rico, siendo su primer Presidente. En el 1951 aprueba los exámenes del Board de Anestesiología.

Pertenece a casi todas las asociaciones médicas existentes, entre ellas: American Society of Anesthesiologists; American College of Surgeons; American Medical Association; Puerto Rico Medical Association y American College of Anesthesiologists. Se convierte en ser el primer puertorriqueño miembro de la American Academy of Anesthesiology formada por la "elite" americana en el campo de la Anestesiología. La entrada es muy selectiva y es solo por invitación. Solo otro puertorriqueño pertenece a esta sociedad, el Dr. E. Colón Yordán, el cual fue recomendado por el Dr. González.

Es también en el 1950 cuando se crea la Escuela de Medicina de la Universidad de Puerto Rico y en el 1952 se comienza a organizar los departamentos clínicos. El Dr.

González es nombrado Profesor de Anestesiología y Director de la Sección de Anestesiología del Departamento de Cirugía. Ocupa dicha posición hasta el 1960 (y en todo este tiempo ocupó dicha posición en nombramiento *Ad-honorem*).

Del 1953 al 1956 presenta tres trabajos en diferentes foros médicos en la isla y estos son: Ventajas y Desventajas en el Uso de Ciclopropano; Anestesia para Procedimientos Urológicos y Anoxia y sus Peligros.

Después de servir a la Escuela de Medicina de la Universidad de Puerto Rico, el Dr. González se dedicó mayormente a la práctica privada de la Anestesiología, pero siempre logrando mantenerse al día en su especialidad. Continuamente también se preocupó de que sus colaboradores hiciesen los esfuerzos de tomar los exámenes del "Board" y/o participaran en actividades académicas.

En el 1958 se da a la tarea de organizar y construir un edificio para oficinas médicas en terrenos del Hospital Presbiteriano (Ashford Medical Building). Este edificio se inauguró en el 1963 y ha sido un éxito.

El Dr. González fue siempre un idealista, luchador incansable, siempre buscador de la verdad y con un sentido humanitario excepcional. Posiblemente, algunas personas lo han catalogado de materialista, pero les puedo asegurar que en él siempre permeaba el deseo de ayudar. No sé como se las arreglaba, pero siempre tenía soluciones para cualquier problema que alguna persona

o amigo le presentase. Una cualidad muy característica de Freddy, a diferencia de la mayor parte de nosotros, era que cuando se encontraba en una situación difícil o de gran estrés, él se crecía y con gran agilidad mental contestaba acertadamente.

Entre otras posiciones que ocupó fue fundador y Director de los Seguros de Servicios de Salud (SSS); miembro Junta de Directores del Hospital Presbiteriano. Presidió el Comité Organizador de Asambleas de la Asociación Médica de P R y en especial, dio una lucha grande en el 1974 cuando el gobierno intentó socializar la medicina en el país. Fue delegado a la American Society of Anesthesiologists de la Puerto Rico Society of Anesthesiologists.

A grandes rasgos estas son algunas de las áreas donde él participó y en todas de forma muy activa. Siempre defendiendo su profesión médica y sobre todo, la salud del paciente.

Era muy madrugador; desde las 6:00 a.m. o antes, estaba llamando y organizando el trabajo del día. Así fue hasta su muerte.

Sobre el Dr. González, podríamos decir muchas cosas más y posiblemente no acabaríamos. Sólo me resta decir que su familia, sus amigos y colaboradores no le olvidarán.

Descanse en paz.

Rosendo Vela, MD

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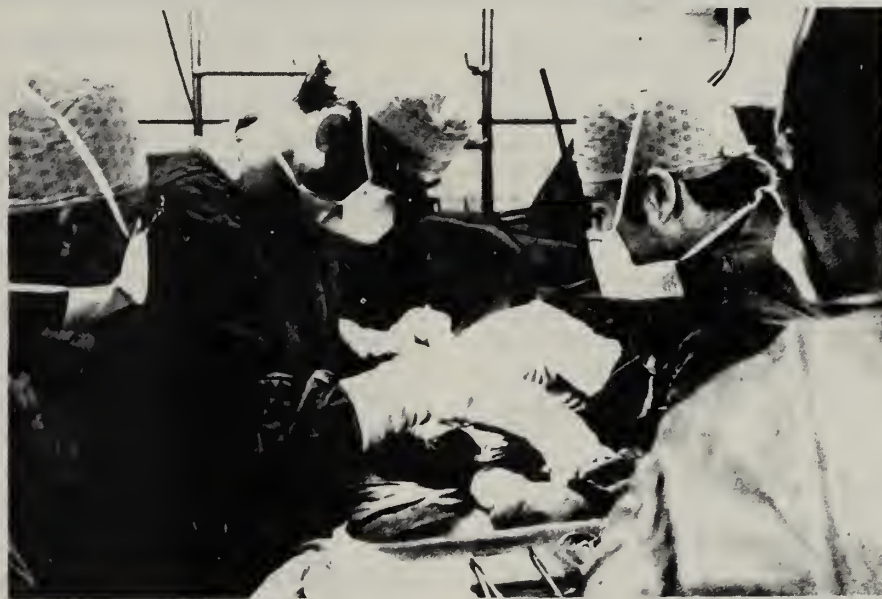
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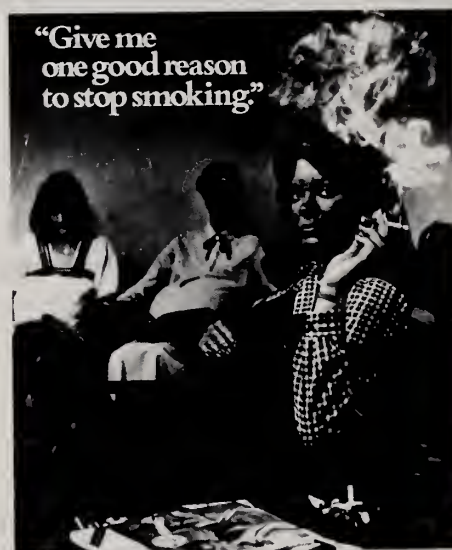
HISTORIA DE LA PSIQUIATRIA PUERTORRIQUEÑA. SIGLO XX

JUAN A. ROSSELLO, M.D.
San Juan, Puerto Rico, 1988, 756 pp.

Una obra que documenta el desarrollo que en este siglo ha tenido la psiquiatría en nuestro país a base de datos provenientes de los periódicos, de comunicaciones oficiales, de estadísticas, listas de conferencias, informes de instituciones etc. El doctor Juan A. Rosselló comienza con una cronología que recoge los hitos en el tratamiento psiquiátrico, incluyendo publicaciones importantes respecto al tema y las fechas en que se establecieron instituciones dedicadas a las enfermedades mentales. El texto se complementa con numerosas fotografías.

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CARTAS AL EDITOR

Liver Biopsy Findings in AIDS

He leído con gran interés el artículo titulado "Liver Biopsy Findings in the Acquired Immunodeficiency Syndrome" escrito por un grupo de distinguidos colegas de la Sección de Gastroenterología y del Departamento de Patología de la Escuela de Medicina de la Universidad de Puerto Rico publicado en el *Boletín de la Asociación Médica* Vol. 80, pp 274-276

Se informa en dicha comunicación de un granuloma causado por *Schistosoma mansoni* en parénquima hepático en uno (1) de ocho (8) pacientes sometidos a biopsia de aguja del hígado para un 12.5% de prevalencia de este tipo de granuloma en pacientes con SIDA.

Los autores comentan que este caso representa una primicia ya que "*Schistosoma mansoni*, a previously unrecognized cause of granuloma in AIDS patients."

Con el deseo de contribuir a este interesante trabajo, traigo a colación una información estadística que presentáramos en una Asamblea de la Asociación Médica en 1958 junto al Dr. Rubén Medina (QEPD) y que nunca se ha publicado.

Se estudiaron 4,000 autopsias consecutivas de pacientes mayores de cuatro años de edad, repasando los protocolos de autopsia y examinando las secciones microscópicas de las mismas. Se eliminaron las autopsias de pacientes menores de cuatro años por entender que no estaban a riesgo de adquirir la enfermedad por su temprana edad que probablemente les hacía inaccesible bañarse en los ríos y quebradas.

Este estudio reveló que 14.8% de dichos casos presentaban evidencia de granulomas de *S. mansoni* en algún órgano, primordialmente hígado o colon. Esta cifra resultaba muy similar a la ofrecida de 15% de puertorriqueños con coprología positiva para *S. mansoni* en los exámenes practicados a los llamados al reclutamiento militar obligatorio durante la segunda guerra mundial. Los casos positivos en esa época eran rechazados para el servicio militar.

En vista de que, a pesar del número limitado de pacientes de SIDA que se le practicó biopsia-hepática, la prevalencia de *S. mansoni* es de 12.5%, nos atrevemos a predecir que en una mayor cantidad de casos de pacientes con SIDA la cifra sería más o menos la misma encontrada por nosotros en la población general.

En un estudio colaborativo de patología de SIDA, donde colaboran la Universidad de Puerto Rico, la Universidad Central del Caribe y el Hospital de Veteranos con el Instituto de Patología de las Fuerzas Armadas, se analizaron 83 autopsias de pacientes puertorriqueños que murieron de SIDA en los Hospitales

Universitarios de la Universidad de Puerto Rico, la Universidad Central del Caribe y el Hospital de Veteranos. El trabajo aun no ha sido publicado, pero la información está disponible y revela que nueve (9) de los ochenta y tres (83) pacientes tenían evidencia anatómopatológica de esquistosomiasis para una prevalencia de 11.0%.

Todo esto nos lleva a pensar que con toda probabilidad el hallazgo del caso publicado, así como los otros nueve casos del estudio colaborativo arriba mencionado, son infecciones de esquistosomiasis adquiridas antes de que estos pacientes desarrollaran SIDA.

Sería necesario un estudio epidemiológico de gran envergadura para explorar si en realidad de adquirir esquistosomiasis aumenta en pacientes con SIDA.

Raúl Marcial Rojas, MD, JD
Presidente/Decano
Universidad Central del Caribe
Escuela de Medicina

Respuesta

Deseamos agradecer al Dr. Raúl Marcial su interesante e informativa carta comentando sobre el artículo "Liver Biopsy Findings in the Acquired Immunodeficiency Syndrome" (*Bol Asoc Med P R* 1988; 80:274-276). Estamos en completo acuerdo con él de que la incidencia de granulomas de Schistosomiasis reportada en nuestra pequeña muestra (12.5%) es la misma que se ha encontrado en estudios previos y no representa una predisposición de los pacientes con SIDA por esta condición. Solo deseamos señalar que en pacientes con SIDA de origen puertorriqueño, se debe tener en mente Schistosomiasis como una causa de granulomas de hígado además de las enfermedades oportunistas que pueden causar este hallazgo.

Será de gran interés conocer los resultados del análisis histopatológico del hígado en la serie colaborativa a publicarse.

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SOCIOS NUEVOS



SOCIOS ACTIVOS

Acosta Rivera, Alejandro MD - Escuela de Medicina Universidad de Puerto Rico, 1982. Oftalmología. Ejerce en San Germán.

Alejandro Benítez, Ausberto MD - Escuela de Medicina Universidad Central del Este, República Dominicana 1979. Medicina Interna. Ejerce en Guayama.

Alvarez Martínez, Nilda J MD - Escuela de Medicina de la Universidad de Zaragoza, España, 1979. Medicina General. Ejerce en Guayama.

Axtmayer Prado, Robert W. MD - Escuela de Medicina Universidad de Puerto Rico, 1984. Medicina de Familia. Ejerce en Bayamón.

Báez Loureiro, Raymond MD - Escuela de Medicina San Juan Bautista, Bayamón, Puerto Rico, 1985. Medicina General. Ejerce en Vega Baja.

Barreto Rodríguez, Marcelino MD - Escuela de Medicina Universidad Central del Este, República Dominicana, 1979. Medicina de Familia. Ejerce en Manatí.

Bocanegra Acevedo, Ubaldo MD - Escuela de Medicina Universidad Central del Este, República Dominicana, 1978. Medicina General. Ejerce en Ponce.

Caballero Torres, Rafael MD - Escuela de Medicina San Juan Bautista, Bayamón, Puerto Rico, 1979. Otorrinolaringología. Ejerce en Guayama.

Carrasco Arias, Angel MD - Escuela de Medicina Universidad de Santo Domingo, República Dominicana, 1964. Medicina General. Ejerce en Guayama.

Cañas Rivas, Luis Rodríguez, MD - Escuela de Medicina Universidad de Sevilla, España, Medicina Interna. Ejerce en Guayama.

Lanaúze Vázquez, Héctor J. MD - Escuela de Medicina Universidad Autónoma de Santo Domingo, República Dominicana, 1984. Medicina de Familia. Ejerce en Peñuelas.

López Hidalgo, Vicente MD - Escuela de Medicina de Puerto Rico 1979. Otorrinolaringología. Ejerce en Hato Rey.

Martínez Rosado, Héctor G. MD - Escuela de Medicina Universidad de Puerto Rico, 1962. Obstetricia y Ginecología. Ejerce en Guayama.

Monroig Pérez, Roberto MD - Escuela de Medicina Universidad de Salamanca, España, 1957. Medicina General. Ejerce en Guayama.

Nido Lanausse, Roque C. MD - Escuela de Medicina Universidad de Zaragoza, España, 1978. Cirugía General. Ejerce en Guayama.

Ortiz Justiniano, Víctor Noel MD - Escuela de Medicina de Puerto Rico, 1968. Cirugía General y Cirugía Pediátrica. Ejerce en Mayagüez.

Pimentel Fernández, José L. MD - Escuela de Medicina Universidad Autónoma de Santo Domingo, República Dominicana, 1972. Cirugía. Ejerce en Guayama.

Rendón Santos, Rafael O. MD - Escuela de Medicina Universidad de Puerto Rico, 1984. Pediatría. Ejerce en Arroyo.

Rivera Figueroa, Marta I. MD - Escuela de Medicina Universidad Central del Este, República Dominicana, 1979. Medicina General. Ejerce en Guayama.

Rodríguez Fontáñez, José MD - Escuela de Medicina Universidad Central del Este, República Dominicana, 1979. Medicina General. Ejerce en Arroyo.

Rodríguez Vázquez, Eduardo MD - Escuela de Medicina Universidad Central del Caribe, Cayey, Puerto Rico, 1980. Cirugía. Ejerce en Vega Baja.

Romero Ruiz, Nereida MD - Escuela de Medicina San Juan Bautista, Bayamón, Puerto Rico, 1984. Medicina General. Ejerce en Arecibo.

Torres Ramos, Carlos M. MD - Escuela de Medicina Universidad de Puerto Rico, 1979. Pediatría. Ejerce en Guayama.

Vázquez Davis, Migdoel, MD - Escuela de Medicina Universidad Central del Este, República Dominicana, 1982. Medicina General. Ejerce en Arroyo.

ACTIVOS ESPECIALES

Santiago de Freytes, Lourdes MD - Escuela de Medicina Universidad Autónoma de Puebla, México, 1982. Pediatría. Ejerce en Mayagüez.

INTERNOS-RESIDENTES

Bacó Bagué, Priscila MD - Escuela de Medicina Universidad de Puerto Rico, 1986. Oftalmología.

Díaz Trancón, Lorena MD - Escuela de Medicina Universidad Autónoma de Guadalajara, México, 1986. Medicina General.

REINGRESOS

Benítez Lorenzo, Pedro L. MD - Escuela de Medicina Universidad de Puerto Rico, 1974. Medicina Interna. Ejerce en Yauco.

Cuevas Alicea, Orlando S. MD - Escuela de Medicina Universidad de Puerto Rico, 1956. Obstetricia y Ginecología. Ejerce en Humacao.

Franceschi Lacroix, Alejandro C. MD - Escuela de Medicina Universidad de Salamanca, España, 1957. Cirugía General. Ejerce en Guayama.

Guzmán Font, Aida MD - Escuela de Medicina Universidad de Puerto Rico, 1956. Psiquiatría. Ejerce en Carolina.

Magraner Folch, Miguel A. MD - Escuela de Medicina Universidad Santiago de Compostela, España, 1957. Ejerce en Arecibo.

Monserate Costa, Salomón MD - Escuela de Medicina Universidad de Puerto Rico, 1961. Cardiología y Medicina Interna. Ejerce en Hato Rey.

Pérez Reilló, Juan José MD - Escuela de Medicina Universidad de Salamanca, España, 1961. Medicina General. Ejerce en Isabela.

Ramírez Costa, Alberto L. MD - Escuela de Medicina Universidad de Puerto Rico, 1970. Urología. Ejerce en Arecibo.

Rivera Badui, José Sandalio, MD - Escuela de Medicina Universidad de Salamanca, España, 1971. Medicina General. Ejerce en Arroyo.

Rodríguez González, Carlos R. MD - Escuela de Medicina Universidad de Madrid, España, 1958. Medicina Interna. Ejerce en Guayama.

ACTIVO NO RESIDENTE

Cano Guerra, René A. MD - Escuela de Medicina Universidad de La Habana, Cuba, 1946. Ortopedia. Ejerce en Miami.

Sirviendo al Pueblo y a la Profesión Médica



ASOCIACION MEDICA DE PUERTO RICO



AMERICAN ACADEMY OF PEDIATRICS

PEDIATRIC AIDS — PREPARE NOW FOR THE FUTURE

Based on his experiences in a Newark-based pediatric AIDS program, a leading pediatric immunologist says by 1991 the number of children infected with the AIDS virus will be in the range of 10-20,000, most with symptoms of AIDS.

Speaking at the American Academy of Pediatrics' (AAP) Medical/Science Writers' Conference, James M. Oleske, M.D., Professor of Pediatrics, Medicine, Pathology and Community Medicine at University of Medicine and Dentistry of New Jersey, Newark, discussed the future of pediatric AIDS.

"There needs to be a commitment of necessary funds to provide disease surveillance, research and clinical care of HIV infected individuals — 12 billion dollars by 1991 — but also a commitment to coordinate a leadership of agencies that are educated, unbiased and compassionate," Dr. Oleske said.

According to estimates, by 1991 one of every ten pediatric beds will be occupied by a child with HIV infection at a cost of almost \$1 billion. These are only in patient costs, he noted.

"The outpatient care requirements of HIV infected children are extensive. Projected out-patient costs for pediatric AIDS by 1991 will exceed \$100 billion," Dr. Oleske said.

"In order to be effective, provision of care must not only provide medical services to the infected child, but also provide the child's mother and family with a wide range of psychosocial support services," Dr. Oleske said.

Based on his hospital's six-plus years of experience in clinical care and research regarding pediatric AIDS, Dr. Oleske's group offered the following recommendations to The Presidential Commission on HIV epidemic:

- The designation and support of centers to provide comprehensive medical and psychosocial services to HIV

infected children and their mothers.

- The establishment of pediatric AIDS day care/respite care centers.

- Establishment of entitlement programs (Medicaid/Medicare) to extend and increase benefits for out-patients services.

- Continued and, as necessary, expansion of the recently established AIDS cooperative treatment groups.

- Recognition by the highest level of government, of the imminent problem HIV infection poses for the foreseeable future.

"It is our intention to educate. This is our best weapon against HIV. Health professionals have an obligation to understand this disease and willingly provide appropriate care to their patients," said Dr. Oleske.

TO LESSEN INFANT MORTALITY: U.S. HEALTH CARE NEEDS MAJOR CHANGES, SAYS EXPERT

A major reordering of the U.S. health care system for children and young families is necessary to reduce the infant mortality rate, according to William H. Hollinshead, M.D., a member of the National Commission to Prevent Infant Mortality.

Dr. Hollinshead, speaking today at the American Academy of Pediatrics (AAP) Medical/Science Writers' Conference, said: "American medical care is long on tests and technology, and often short on prevention, guidance and support. We must reorder the emphasis, making the caring capacity of parents our first investment and concern."

"The system today is so fragmented, complex, inequitable, ineffective and expensive that it cannot do much for many of the kids who most need help," said Dr. Hollinshead, who is Medical Director and Chief, Division of Family Health, Rhode Island Department of Health, Providence.

The National Commission to Prevent Infant Mortality, formed in 1987 to develop a national strategy to reduce infant mortality, will report to the President and Congress this summer, urging setting a goal for the healthiest children in the world by the year 2000. "With the technology and knowledge at hand, we can reduce infant losses among all groups of children in the U.S. We don't need more research before we can act," Dr. Hollinshead said.

Infant mortality is the death of children before their first birthday, and higher rates can be the "tip of the iceberg," pointing to the existence of larger problems such as low birthweight, disabilities and serious illnesses.

In 1955, the U.S. had the sixth best infant mortality rate and Japan the seventeenth. By 1985, Japan was first, and we had fallen to eighteenth.

Dr. Hollinshead, also Clinical Assistant Professor of Community Health at Brown University, mentioned

specific health areas that need to be altered, urging support from employment policies, insurance coverage, child care, the media and government.

"Our best and most cost effective efforts are often unavailable to the children who need them most. There are large numbers of mothers and children who cannot find or cannot see a doctor. We must make it much easier to get Medicaid coverage, and we must be sure that families with Medicaid coverage have access to the care we've promised," he said.

"Thus, America has an increasingly visible problem with infant health, with weakened child health programs, and no real national policy on children's health and development. Unfortunately, we must look for solutions in an environment of breathtaking national deficits," Dr. Hollinshead said.

AAP CONDEMNS USE OF STEROIDS

The American Academy of Pediatrics (AAP) has condemned the use of anabolic steroids by athletes because of their known toxic side effects and the belief that the use of these drugs is "just another form of cheating."

The AAP's Committee on Sports Medicine, in a policy statement in the August issue of *AAP News*, says it deplores the use of anabolic steroids by both professional and amateur athletes who use steroids to increase muscle strength and/or muscle size.

The AAP urges physicians performing preparticipation sports physicals to ask questions regarding steroids, particularly if the patient competes in one of the sports most associated with steroid misuse. "Even if the athlete denies using anabolic steroids, anticipatory guidance concerning their side effects is appropriate for youths at risk," the committee says.

"Competitors who enhance their athletic performance with anabolic steroids put the other competitors in the difficult position of either not taking them and conceding a perceived advantage to the abusing competitor, or taking them as well and accepting the risks of untoward side effects. Young athletes should not be placed in the situation of having to make such a choice," the committee says.

The use of steroids is widespread among professional and college-level athletes, particularly football players and weight lifters, the committee says. These illicitly obtained drugs are "readily available to athletes of almost any age," according to the statement.

The potential complications of steroid use include adverse effects on the liver, including tumors; a decrease in serum high-density lipoprotein levels, possibly increasing the risk of coronary artery disease; and harmful effects on male sperm and hormone production. A common side effect in women is virilization. Psychological changes attributed to steroids include mood swings, aggressive behavior and changes in libido.

The committee calls steroid misuse a "major problem" in both professional and elite amateur athletics. In 1976,

the International Olympic Committee on Drugs banned the use of anabolic steroids by competitors and placed severe sanctions on violators. In 1984, the American College of Sports Medicine unequivocally condemned the use of steroids as performance-enhancing drugs.

BICYCLE HELMET COALITION FORMED

The American Academy of Pediatrics (AAP) has joined forces with the National Head Injury Foundation (NHIF) and the Bicycle Federation of America (BFA) to increase awareness and use of bicycle helmets and reduce head injuries in children.

"The newly-formed Bicycle Helmet Coalition allows the Academy to continue its long-standing commitment toward reducing accidents and injuries in children," said Richard Narkewicz, M.D., AAP president.

Head injuries are the number one cause of death and disabling injuries in bicycle accidents. The use of helmets could prevent more than half of the 1000 annual bicycle fatalities in the U.S.

The three organizations in the coalition have a history of advocacy for bicycle safety. The AAP's injury prevention program always has included bike safety; the BFA has worked with manufacturers and advertisers since 1977 to promote helmet use and other safety issues; and the NHIF's Traumatic Head Injury Awareness and Prevention program has focused primarily on bicycle helmet use.

A brochure on bicycle safety, "Protect Your Head: Where would you be without it?" is available to viewers or readers with a business-sized, stamped, self-addressed envelope sent to: Bike Brochure, American Academy of Pediatrics, Dept. C, P.O. Box 927, Elk Grove Village, IL 60009.

ACELLULAR DTP VACCINE PRODUCES FEWER REACTIONS

Swedish researchers studying the acellular diphtheria-tetanus-pertussis (DTP) vaccine have found that this form of the vaccine, as opposed to the whole cell vaccine used currently in the U.S., produced fewer local and systemic reactions in the infants studied. In addition, the acellular vaccine appeared to produce a better rate of immunologic response.

Published in the September issue of *Pediatrics*, the journal of the American Academy of Pediatrics (AAP), a study in Sweden found that fever and redness at the injection site occurred in significantly fewer infants who received the acellular vaccine. Fever occurred in six to eight percent of the acellular vaccinees, as opposed to 25 percent of the whole cell vaccinees; redness appeared in two to 13 percent of the acellular vaccinees compared with 24 to 32 percent of the whole cell vaccine recipients.

"However, the efficacy in preventing pertussis in this study was only moderate and no particular immunologic

response could be correlated with protection. Therefore, further studies are in progress to determine whether the acellular vaccine can really substitute for the whole cell vaccine," said Stanley Plotkin, M.D., Chairman, AAP Committee on Infectious Diseases.

"The present position is that the acellular vaccine clearly causes fewer local reactions than the whole cell vaccine but may not give as much protection. Further comparisons are necessary," Dr. Plotkin said.

The whole cell DTP vaccine used in the U.S. has been criticized for its high reaction rate. In 1979, general immunization with the DTP vaccine in Sweden was discontinued "because of insufficient efficacy and growing public concern about serious adverse reaction," according to the researchers, from Sachs' Children's Hospital and the National Bacteriological Laboratory in Stockholm.

The study, begun in 1984, tested a Japanese two-component vaccine on 319 six-month old infants. This vaccine had not previously been studied extensively in children less than two years of age. Doses of whole cell and acellular vaccines were administered, as well as placebos. Doses were not given to infants who had acute infections, high fevers or ones who had serious adverse reactions to previous doses.

"Whole cell vaccinees reported significantly more of all of these systemic reactions (fever, fretfulness, excessive sleeping) than the acellular vaccinees and the recipients of the aluminum-containing placebo solution," the researchers wrote. "Persistent crying of any duration was more frequent in whole cell recipients after the first two doses. This reaction was rare among the acellular and placebo vaccinees."

The researchers noted that local reactions were few but did increase as the number of doses increased. In 231 recipients of two or three doses of the acellular vaccine, only two reactions contraindicating further doses occurred. "Neither the design nor the size of the study allows for a conclusion concerning a causal association," the researchers said.

The researchers also said that even one dose of the acellular vaccine gave an enhanced antibody response (84 percent) than three doses of the whole cell vaccine, when blood samples from the infants were collected two months later.



BRIEF SUMMARY

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate.

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

OVERDOSAGE

There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

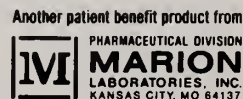
While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED

CARAFATE (sucralfate) 1-gm tablets are supplied in bottles of 100 (NDC 0088-1712-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1712-49). Light pink scored oblong tablets are embossed with CARAFATE on one side and 1712 bracketed by C's on the other. Issued 1/87

Reference:

1. Eliakim R, Ophir M, Rachmilewitz D: *J Clin Gastroenterol* 1987;9(4):395-399.








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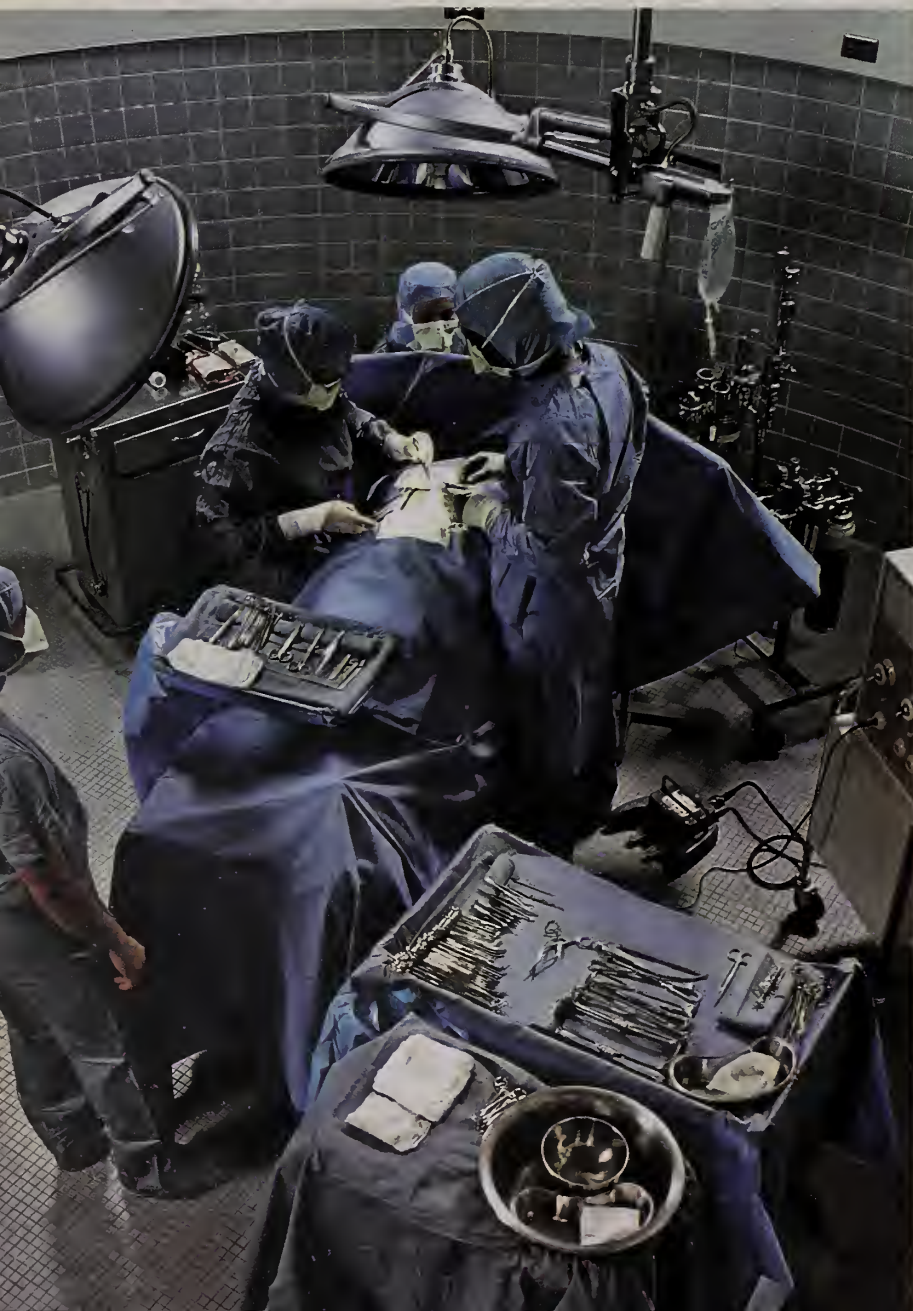
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AMA REPORT: FUTURE OF THE FAMILY PRACTICE PHYSICIAN

A shortage of family practice physicians will occur if increasing support from the medical profession is not forthcoming, concludes a report in JAMA.

The report by the AMA's Council on Long Range Planning and Development found that despite greater demand for family practice physicians, the specialty suffers from a lack of recognition both publicly and professionally. The study, covering the years 1965 to 1986, shows the number of U.S. family physicians gradually increased through 1986 but did not keep pace with the number of physicians overall.

"There may be a shortage of family physicians, despite a predicted over-supply of physicians in general, particularly in managed-care systems and in rural areas that are underserved," concludes the report.

The report identifies several key areas that will affect the future of family practice, including professional and public image, graduate medical education, reimbursement, managed care, professional liability, and ethics. "To ensure the continued growth of this specialty, family practice will need to continue its efforts to disseminate information about its attractions to all levels of the profession, particularly medical students," it says.

Despite a lack of physicians specializing in family practice, the report predicts an increase in demand for family physicians due to the popularity of health maintenance organizations, which use family and general practice physicians for primary care and referral. The authors see new opportunities for family physicians as primary care providers because of "the dramatic increase in managed care systems in recent years."

"There does not seem to be a widespread public understanding that family practice is a *bona fide* specialty. Although more and more patients are interested in having a single physician as the provider of primary care... there is a perception that this type of physician no longer exists," the report says.

One explanation for the shortfall is an average income for family practice physicians of \$80,330, compared with \$119,000 for all physicians. Their fees average \$23.48 compared with \$30.10 per visit for the profession. Family practitioners work one week more per year and see more patients, 139.2 versus 117.7, each week than do their

colleagues. Patients are able to see a family physician in 2.7 days compared with 6.2 days for the average physician.

The report says approximately 60 percent of visits to a family physician are by women, primarily in their child-bearing years, creating competition with obstetricians and gynecologists. However, it suggests the increase in average life span will result in "a noticeable shift in their services" to accommodate the health care needs of an older population.

Pointing to a recent survey of hospitals, the authors conclude that family physicians are in greater demand nationwide than any other medical specialty. The greatest demand is in the Midwest, where 40 percent of all responding hospitals reported a need for family specialists. The study indicates physician population increased by almost 45 percent between 1975 and 1986, while the number of family physicians grew by only 24 percent. The AMA further projects the total physician population by the year 2001 will increase by nearly 22 percent, but family physicians by only 9 percent.

The Council cites a decrease in residency programs as a roadblock to generating new sources of graduate medical physicians in family practice, and suggests this specialty "may wish to explore the question of corporate funding for family practice residency training programs. The medical profession must strive to ensure that family practice residency programs... are of the highest quality and that graduates of these programs have been trained to deal with the complex ethical issues they will face throughout their professional careers."

JAMA September 2, 1988

MONONUCLEOSIS: OCCUPATIONAL HAZARD IN HOSPITALS?

A Belgian physician, in the "Questions and Answers" section of JAMA asks whether infectious mononucleosis can be considered an occupational hazard for hospital staff. Not likely, respond Stephen E. Straus, MD, and David Henderson, MD, of the National Institute of Allergy and Infectious Diseases, Bethesda, Md. Ninety percent of infectious mono cases are caused by the Epstein-Barr virus (EBV), which is very difficult to transmit (transmission mainly occurs through intimate exchange of saliva), say Straus and Henderson. They support recommendations that infectious mono patients not be isolated and that EBV not be considered a substantial occupational hazard. Infection control measures "should further reduce the minimal additional risk of acquiring EBV infection that exists for health care workers," they say.

JAMA September 2, 1988

STUDIES MIXED ON EFFICACY OF *HAEMOPHILUS INFLUENZAE* B VACCINE

Three studies in *JAMA* report puzzling contradictory results on the efficacy of a vaccine to prevent *Haemophilus influenzae* type b (Hib) infections, a leading cause of bacterial meningitis and other serious illnesses in young children.

Two studies found the *Haemophilus influenzae* polysaccharide vaccine (HBPV) effective in protecting young children from Hib, but disagree on the degree of protection. The third study, however, suggests the vaccine provided children no clinical protection and may even have increased their infection risk.

Once mistakenly believed to be the cause of epidemic influenza (for which it was named), Hib is a major cause of serious systemic illness among children in the United States, where it affects about one of every 200 children by age five. The bacterial disease is believed to be transmitted from person to person, especially among young children within households and day-care facilities.

In April 1985, the HBPV was licensed in the U.S. after a large clinical trial in Finland showed it 90 percent effective in protecting children aged 18 to 71 months. But since the vaccine's introduction, reports of immunization failures have led to doubts about its effectiveness and concern that it may even increase a child's Hib risk.

In one of the *JAMA* studies, Lee H. Harrison, MD, of the Centers for Disease Control (CDC), Atlanta, and colleagues found evidence that the vaccine may be considerably less effective than found by the Finnish trial. The study examined cases of invasive Hib disease among children aged 18-59 months attending day-care facilities. Of 126 Hib cases reported, 17 percent had been vaccinated, compared with 28 percent of 291 matched, uninfected controls. Areas involved in the study—Missouri, New Jersey, Oklahoma, Tennessee, Washington, and Los Angeles County—have a total population of 34 million and represent substantial geographic, racial, and urban-rural diversity, the authors say. They found no evidence that Hib-infection risk was increased in the week after vaccination and estimate the vaccine's efficacy at about 45 percent—about half as high as reported in the Finnish study.

A second *JAMA* study compared the vaccination histories of Hib-infected children in Connecticut, Dallas County, and greater Pittsburgh with the vaccination histories of uninfected controls. Of 76 children aged 24 to 72 months, from whom Hib was isolated, 12 percent had been vaccinated, compared with 39 percent of 152 matched, uninfected controls, say the authors, Eugene D. Shapiro, MD, of the Yale University School of Medicine, New Haven, Conn., and colleagues. They estimate the vaccine's protective efficacy at 88 percent overall, 91 percent for the Connecticut children, 92 percent in Dallas county, and 81 percent in greater Pittsburgh. They conclude that HBPV "is highly effective in these areas among children who receive the vaccine

when they are 24 months of age or older."

The third HBPV study examined the vaccine's efficacy among Minnesota children. Originally part of the study by Shapiro and colleagues, it was later separated due to its dramatically disparate findings, even though both used the same protocols and similar surveillance and analysis methods, say authors Michael T. Osterholm, PhD, MPH, of the Minnesota Department of Health, Minneapolis, and colleagues.

During the first 28 months that the vaccine was used in Minnesota, 88 cases of invasive Hib disease were identified in children aged 24 to 71 months, the group targeted for vaccination, the authors report. Of the 88 cases, 36 (41 percent) had been vaccinated, while out of 176 matched, uninfected controls, only 58 (33 percent) had been vaccinated. The researchers report a -55 percent protective efficacy for the vaccine, which suggests an increased infection risk, although they say it is possible that chance alone could explain the excess infections among vaccinated children. "Our results indicate that type b polysaccharide vaccine has had minimal or no impact on the prevention of *H influenzae* disease in Minnesota children and may even be associated with an increased risk of disease," they conclude.

In an accompanying editorial, Edwards A. Mortimer, Jr., MD, of Case Western Reserve University School of Medicine, Cleveland, Ohio, discounts the likelihood that methodological differences are behind the disparate results of these and other HBPV efficacy studies. He suggests that biological factors are probably the answer to the enigma; for instance, differences between strains of Hib prevalent in the different areas could explain the disparate findings.

"In view of these uncertainties, it is not easy to be entirely confident of recommendations to those who provide health care to children and who feel considerable discomfort over this turn of events," he concludes. "However, like it or not, we must often make decisions in the absence of incontrovertible evidence." He discusses a newly licensed improved "conjugated" Hib vaccine that appears to induce higher antibody levels and may be more effective in younger children. Because of the enhanced immunogenicity of the new vaccine and his belief that the probable benefits outweigh the costs and risks, if any, Mortimer recommends that pending further data, the newer vaccine should be used for children beginning at 18 months of age.

A related fourth study in *JAMA* describes a cluster of Hib infections among adults in a nursing home and an adjoining hospital. Primarily a disease of young children, most adults are believed to be immune to Hib infections and outbreaks of disease among adults appear to be uncommon, say the authors, Perry F. Smith, Now of the New York State Department of Health, Albany, and colleagues. All six case patients had personal contact with at least one other case-patient. "This cluster of disease suggests that elderly adults may be more susceptible to *H influenzae* infection than is generally recognized and that outbreaks among adults may result from person-to-person transmission," they conclude.

JAMA September 9, 1988

GENITAL ULCERS IMPORTANT HIV RISK FACTOR IN GAY MEN

Genital ulcerative diseases appear to be an important risk factor for human immunodeficiency virus (HIV) infection in homosexual men, reports a study in JAMA.

In the report, authors Walter E. Stamm, MD, and colleagues at Harborview Medical Center and the University of Washington School of Medicine, Seattle, note that recent studies have shown an association between genital ulcer disease and AIDS-causing HIV infection among highly sexually active heterosexual populations in Africa. The authors say their data suggest that the same link may hold for homosexual men in the United States.

Herpes simplex virus (HSV) infection and syphilis are the two most common causes of genital ulcers in gay men in the U.S., so the authors looked at the association between these two diseases and HIV infection in 200 men enrolled between 1983 and 1986 in a study of acute proctitis. HIV infection was independently associated with a history of syphilis, serologic evidence of syphilis, a history of HSV infection and antibodies to HSV-2 (genital herpes). But it was not associated with a history of other, non-ulcerative genital infections or with antibody to *Chlamydia trachomatis* or HSV-1. Similar associations were observed in 111 asymptomatic homosexuals seen for HIV screening.

"Historical or serological evidence of either of these diseases was associated with threefold to eightfold increased HIV infection among the homosexual men we studied," the researchers report. "These observations did not simply reflect increased sexual activity in the HIV-infected group, because they persisted after adjustment for indexes of sexual activity..."

Genital or anorectal ulcers are "logical cofactors" to facilitate HIV transmission or acquisition, the researchers say, and may do so in several ways. First, such ulcers may provide a portal of entry or exit for HIV. In addition, both HSV and the syphilis-causing bacteria stimulate immune system cells that, in vitro, have been shown to be more susceptible to HIV infection than unstimulated cells.

"Our observations may have important implications for the prevention of HIV transmission," the authors conclude. "Early diagnosis and treatment of syphilis and comprehensive contact investigation might reduce the transmission of HIV. Similarly, counseling regarding the possible risk of HIV acquisition during recurrent genital or anorectal herpes, abstinence during recurrences, or even giving prophylactic acyclovir to persons who suffer frequent recurrences may contribute to the control of HIV. Prompt treatment of syphilis and herpes with penicillin and acyclovir, respectively, might reduce the period of susceptibility to HIV of viral shedding from ulcerative lesions."

JAMA September 9, 1988

MUMPS IN THE WORKPLACE

The number of reported mumps cases in the U.S. has more than quadrupled since 1985 after a 20-year decline, and the age of those affected has shifted upward. Now, a report in JAMA describes the first documented mumps outbreak in the workplace—119 cases seen among employees at three Chicago futures exchanges and their household contacts in 1987. The report, by Karen M. Kaplan, MD, of the Centers for Disease Control, Atlanta, and colleagues, says 21 patients developed complications, nine were hospitalized, and direct and indirect economic costs associated with the outbreak totaled nearly \$121,000. Noting that only three patients had documented mumps immunization, the authors call the outbreak "consistent with the recent changing epidemiology of mumps and the increase in reported cases in the adolescent and young adult populations." A cohort of adolescents and young adults "underimmunized against mumps and underexposed to disease" is now entering the work force, they say, recommending that susceptible employees be vaccinated.

JAMA September 9, 1988

FATAL FOOD-INDUCED ANAPHYLAXIS

Fatal cases of food-induced anaphylaxis, a severe allergic reaction, are rarely reported, but a study in JAMA describes seven such cases identified over the past 16 months. The authors, John W. Yunginger, MD, of the Mayo Medical School, Rochester, Minn., and colleagues, say the victims included five males and two females and ranged in age from 11 to 43. All seven had experienced a number of previous anaphylactic episodes after eating the food responsible for their allergic reactions—peanuts in four cases, and pecans, crab and fish in one case each. Six cases occurred away from home. In none of the cases studied, however, was injectable epinephrine administered immediately after the victims began to experience symptoms of the food reaction, the authors say. "Food-sensitive individuals must self-administer epinephrine promptly at the first sign of systemic reaction," they say.

JAMA September 9, 1988

TRANSDERMAL CLONIDINE HELPS SMOKERS QUIT: REPORT

Research suggests that the antihypertensive drug clonidine may help smokers kick the habit by reducing their craving for cigarette. A report in September's *archives of Internal Medicine* now says this effect also is seen when the drug is administered in a transdermal

form—a patch that delivers clonidine into the bloodstream through the skin. Steven A. Ornish, MD, now in private practice, and colleagues at the University of California, San Diego, School of Medicine looked at transdermal clonidine's effect on withdrawal symptoms in a double-blind, placebo-controlled study involving 40 smokers. Subjects were told to maintain their usual cigarette intake for three days, then stop smoking for the next three. Compared with those receiving transdermal clonidine, the placebo group experienced more withdrawal symptoms such as craving, irritability, anxiety, restlessness and hunger during the three-day cessation period, the study says.

SURGEONS NEED TO BE ON GUARD FOR CHILD ABUSE, REPORT SAYS

A study in September's *Archives of Surgery* say surgeons caring for injured children can help spot child abuse by recognizing the characteristic features distinguishing accidental from intentional injuries. This is especially true in the case of abdominal injuries, report Daniel E. Ledbetter, MD, of Children's Hospital and Medical Center, Seattle, and colleagues, who reviewed the cases of 156 children who suffered abdominal injuries—89 percent in accidents, 11 percent though abuse. The abused children were younger than the others and had injuries unexplained by their medical histories. In addition, while 61 percent of the accident victims suffered injuries to a single, solid abdominal organ, 65 percent of the abused children had intestinal tract injuries. "Surgeons who care for injured children need to have a high degree of suspicion for abuse, especially in younger children," the authors conclude.

HUMAN HAIR FORM

It's long been thought that the cross-sectional shape of the human hair shaft is what makes a hair curly, wavy, or straight. But not so, researchers report in September's *Archives of Dermatology*. Bernt Lindelof, MD, of the Karolinska Institute, Stockholm, Sweden, and colleagues say it is actually the form of the hair follicle that determines hair form. The authors used three-dimensional, computer-aided reconstruction to study serial sections of human hair follicles from 10 patients—five whites, four blacks and one Oriental. The authors say the analysis determined that the hair follicle was helical in the case of the black subjects and completely straight in the case of the Oriental. For the white subjects, the follicles represented variations between these extremes. "Apart from purely academic interest, these results may explain failures in cosmetic electrolysis elimination of unwanted hair growth," the report concludes.

PHYSICIANS NEED BETTER TRAINING ON PRESCRIBING NICOTINE GUM: STUDY

Many internists have misconceptions about the use of nicotine gum for smoking cessation, indicating widespread need for physician education about its proper use, says a study in JAMA.

The report, on how internists currently prescribe nicotine gum and other drugs for smoking cessation, is accompanied by three other studies on smoking cessation approaches using nicotine gum to help smokers quit.

In a random survey of 208 internists in the San Francisco Bay Area, physicians reported prescribing nicotine gum to fewer than 25 percent of patients trying to quit smoking, say the authors, Steven R. Cummings, MD, of the University of California Medical Center, San Francisco, and colleagues. Previous studies have shown the gum to be a useful aid in helping smokers quit, the authors report. However, "surveys by the manufacturer suggest that most prescriptions of nicotine gum are given with little or no instruction about how to use the gum and little or no counseling or follow-up about quitting smoking."

Contrary to the manufacturer's recommendations and expert opinion, nearly half the internists believed smokers should be told to use the gum to reduce the number of cigarettes they smoke if they could not quit. "Continued smoking while using the gum may produce higher serum concentrations of nicotine than smoking alone, and this might increase the risk of nicotine-related adverse effects," they report.

Twenty percent of internists incorrectly thought that patients should be advised to "swallow the juices from the gum so that the nicotine can be absorbed from the stomach," they report. The knowledge that nicotine is absorbed mainly through the mucosa of the mouth rather than the stomach, is fundamental to the optimum use of the gum. "Patients should chew slowly and intermittently and should allow time for the nicotine to be absorbed from the buccal mucosa."

Also contrary to manufacturer's recommendations, 24 percent of internists said patients should not use the gum longer than one month and only a few believed that gum use should continue after three months. "Smokers have a high risk of relapse in the first year after quitting, especially during the first three months," the authors say. "For this reason it has been recommended that patients continued to carry the gum with them and use it as needed for at least three months." While the manufacturer recommends that it be used no longer than six months, other experts suggest some patients may benefit from more prolonged use of nicotine gum and that the length of therapy should be individualized.

"Sedatives are not approved or recommended for use as an aid to quitting smoking," the authors say. "Nevertheless, almost one fourth of internists said that they had prescribed sedatives for this purpose during the previous year." The authors believe their study accurate.

tely represents the opinions of internists in the San Francisco area, though it may underestimate the degree of physician misinformation throughout the United States. Since the internists studied are near larger medical schools with active continuing education programs, they may be better informed about gum use than internists elsewhere, they conclude. "Nicotine gum is an effective adjunct for smoking cessation in smoking-cessation programs but has been less effective when used in medical practices. This may be due in part to inadequate instruction from physicians about how to use nicotine gum."

In a related study of 538 patients at a smokers clinic who had been prescribed nicotine gum, 6.3 percent still were using gum after one year, say the authors, Peter Hajek, PhD, of the University of London Institute of Psychiatry, England, and colleagues: "This group represented 25 percent of lapse-free abstainers."

For many able to quit, long-term use of gum was likely an essential ingredient of their success. Those who succeeded without using the gum were significantly lighter, less-dependent smokers. The authors also found that long-term gum users gained significantly less weight than those who used other strategies to quit, although, being heavier smokers, they should have gained more.

Although some heavy smokers who manage to quit with the help of the gum may continue to use it beyond one year, the authors conclude that recommending the gum remains well justified: "At least some of the disadvantages of not being able to stop using nicotine completely are balanced by the lessening of weight gain." Giving gum to smokers can't create nicotine dependence but will substitute a different source of the drug—and gum contains no tar, carbon monoxide, or other harmful tobacco smoke components and does not pollute the air, they add.

In another *JAMA* study, authors Stephen P. Fortmann, MD, and colleagues at the Stanford University School of Medicine, Palo Alto, Calif., report on the effectiveness of a minimal contact treatment program using nicotine gum. The Stanford Stop Smoking Project studied 600 smokers divided into four groups: one group received no gum, a second was given placebo gum, a third received gum with instructions to take a fixed dose on hourly schedule, and the fourth received gum and instructions to chew it when they had an urge to smoke. All participants also received weekly relapse prevention modules by mail.

The researchers found that abstinence rates (at least seven days) at six-months follow-up were 31 percent in both groups given nicotine gum compared to 22 percent for those on placebo and those not getting gum. Relapse rates in the two nicotine gum groups were about half those in the placebo and no-gum groups. Nicotine gum "may be a useful adjunct to minimal contact smoking cessation formats, which have broad appeal," and such minimal contact programs may assist physicians in helping patients use nicotine gum more effectively, they conclude.

A fourth *JAMA* study examined the success rates of family physicians using different smoking cessation strategies. Eight-three physicians were randomly divided into three groups, say the authors, Douglas M. Wilson, MD, of the McMaster University Medical

Center, Ontario, Canada, and colleagues. In a gum-only group, physicians were asked to speak to patients about smoking cessation and offer nicotine gum. In a "gum plus group," physicians received intervention training that involved advising patients to stop smoking and to set a quitting date, and offering them nicotine gum along with four follow-up visits. The third group received only the care they usually would have received. Using at least three months of abstinence as a criterion, the authors found 8.8 percent of the gum plus training group had stopped smoking compared with 6.1 percent of gum only and 4.4 percent of patients who had received usual care.

JAMA September 16, 1988

NEW RADIOLOGY CONTRAST AGENTS SAFER BUT MORE EXPENSIVE

The dye-like contrast media long used in various radiology procedures have always caused a certain percentage of adverse reactions, ranging from nausea to death. A recently developed class of contrast agents, called low-osmolar contrast media (LOCM), can greatly reduce this risk, but at high cost—raising a host of medical, economic, legal, and public policy issues about the use of such a technological innovation, an analysis in *JAMA* says. The report, by Peter D. Jacobson, JD, MPH, and C. John Rosenquist, MD, of the RAND Corp., Santa Monica, Calif., says the new LOCM are equally effective in diagnostic radiology as traditional high-osmolar contrast media and "almost certainly safer," yet approximately 12 to 15 times more expensive. If used in all cases requiring contrast injections, the new agents could cost nearly \$1 billion extra annually, the authors say. "Our cost-effectiveness analysis and an analysis of the medical evidence suggest that LOCM should be limited to high-risk patients," they write. "We conclude that the medical profession should take the lead in developing protocols for appropriate assessment, reimbursement and use of LOCM." An accompanying editorial by Harry W. Fischer, MD, of the University of Rochester (NY) Medical Center acknowledges the difficult issues raised in the RAND analysis. He calls the proposal to limit the use of LOCM a solely economic argument. Although saying that improved patient safety—not just comfort—is the only way to justify the new agents' greatly increased cost, he also notes that "the physician is not accustomed to putting national economic considerations above the patient's welfare."

JAMA September 16, 1988

ACYCLOVIR PREVENTS RECURRENCE OF SUN-INDUCED COLD SORES IN SKIERS

People suffering from herpes simplex labialis (oral/facial herpes lesions like cold sores) can be plagued by a recurrence of this infection when skiing at high altitudes,

presumably because of exposure to ultraviolet radiation. But a study in JAMA reports that the antiviral drug acyclovir can prevent reactivation of oral/facial herpes in skiers. The study, by Spotswood L. Spruance, MD, of University of Utah School of Medicine, and colleagues, involved 147 people with a history of sun-induced herpes recurrences. They were treated prophylactically with oral acyclovir or a matching placebo and then studied during their ski holidays. Five (7 percent) of 75 acyclovir-treated subjects developed herpes lesions compared with 19 (26 percent) of 72 in the placebo group. "Most of the lesions that we observed occurred on the lips, a location notoriously difficult to protect with sunscreens," notes the study, supported by a grant from the Burroughs Wellcome Co., Research Triangle Park, NC, maker of the drug used in the research.

JAMA September 16, 1988

"FAILURE TO THRIVE" CAN BE MISLEADING

The vague concept of "failure to thrive" can mislead physicians and parents, even to the point of inappropriate care, warns a report in September's *American Journal of Diseases of Children, AJDC*. The report's author, Gunnar B. Stickler, MD, of the Mayo Clinic, Rochester, Minn., makes the point by describing the "medical oddyssey" of two infants who, because they were growing slowly during their first 18 months of life, underwent numerous diagnostic tests. Eventually, due to "the concept that higher energy intakes result in greater increases in length," each infant had a gastrostomy—placement of a surgical opening into the stomach for nutritional purposes. Increases in weight resulting from gastrostomy feedings had no effect on growth in length, yet "it was very difficult to convince the parents that the gastrostomies were not necessary... A great deal of reassurance and even hospitalization were necessary before they could be convinced that the child would not starve," Stickler writes. In fact, he notes, both children were developing appropriately—they were simply short. "The term 'failure to thrive' continues to be used despite warnings that its use may lead to misunderstanding and even mismanagement," he concludes.

NEW CONCEPT IN RECONSTRUCTION OF MALFORMED EAR

A report in September's *Archives of Otolaryngology-Head and Neck Surgery* describes a new technique for treating microtia, a rare condition in which the external part of the ear is deformed and the opening to the auditory canal doesn't develop properly. The condition, seen in one in 10,000 births, causes more emotional distress in young children due to the ear deformity than the hearing loss involved, notes the report's author, Robert O. Ruder, MD, of the University of California, Los Angeles.

"Reconstruction of the severely deformed external ear has been a frustrating experience for many patients and surgeons alike," Ruder writes. "Until recently, children with microtia... have been subjected to multiple procedures with frequently ungratifying results." But a recently developed, four-stage surgical technique involving a graft sculpted from a piece of rib cartilage can be used to rebuild the deformity with a good cosmetic outcome, the author writes. The surgery should begin by age 5, says Ruder, who notes that he has performed the surgery in 13 patients over the past four years with "gratifying results."

TEACHING HIGH SCHOOLERS HOW TO PREVENT CARDIOVASCULAR DISEASE

School-based primary prevention program may be effective in educating adolescents about risk factors for cardiovascular disease (CVD) and may help them acquire heart-protecting habits, says a study in JAMA.

There is a clear need for school programs to help steer young people away from lifestyles that raise their risk of developing heart disease, say the study's authors, Joel D. Killen, PhD, of the Stanford University School of Medicine, Palo Alto, Calif., and colleagues. Sizeable numbers of children and adolescents in the United States are overweight and show evidence of high blood cholesterol levels. Many smoke cigarettes, eat too much fat and cholesterol, and don't get regular exercise. These factors increase their risk of hypertension, atherosclerosis, and early death.

The authors studied the effect of a school-based CVD risk reducing program on 10th-grade students at four randomly selected northern California high schools. Students at two schools served as a control group while students at the other schools received 20 classroom sessions of instruction in risk reduction. The program was divided into five modules: Physical activity, nutrition, cigarette smoking, stress, and personal problem solving. The results, the authors say, are very encouraging.

At a two-month follow-up, researchers found that knowledge of CVD risk factors increased an average of 50 percent among students in the treatment group. While there was no significant differences between the groups in the proportion of regular smokers who quit at follow-up, more students (28.5 percent) in the treatment group who were "experimental" smokers before treatment reported quitting compared with 17.6 percent of experimental smokers in the control group. In addition, only 5.6 percent of the experimental smokers receiving training graduated to regular smoking, compared with 10.3 percent in the control group, the authors say.

Also at follow-up, 30.2 percent of treated students who did not exercise regularly before the intervention program reported regular physical activity, compared with 20 percent of non-exercisers in the control group. The strongest and most consistent physiological change was in the resting heart rates of students in the treatment

groups, which decreased and average of 2.3 beats per minute for boys and 4.1 for girls, compared with an average increase of 0.4 beats per minute for both boys and girls in the control group. "This finding is encouraging, since resting heart rate provides a reasonably good index of physical fitness," the authors say.

Treated students were also more likely to report that they would choose "heart healthy" snack items than students in the control group. Reductions in body fatness was also achieved, although the program's impact was consistent only for girls.

"Taken together, the findings indicate that potentially effective CVD risk-reduction training may be provided to a large segment of the population through school-based primary prevention education," the authors conclude. "It is unclear whether the gains observed in the treatment group will be maintained over a longer period of time. However, it would seem reasonable to integrate risk-reduction programs into the general school curricula at more than one grade level to achieve maximum benefit."

JAMA September 23, 1988

SLEEP DEPRIVATION DOESN'T APPEAR TO AFFECT RESIDENT PERFORMANCE: STUDY

Sleep deprivation caused by usual hospital on-call schedules doesn't appear to impair the cognitive and motor performance of medical residents or their ability to care for patients, concludes a study in *JAMA*.

There has been considerable concern that lack of sleep experienced by interns and residents on long shifts may endanger patients in their care. Prolonged sleep loss has been shown to adversely affect cognitive function and behavior. What is unclear is whether sleep deprivation resulting from usual hospital call schedules can cause such deleterious effects, say the study's authors, Timothy F. Deaconson, MD, of the Medical College of Wisconsin, Milwaukee, and colleagues.

The authors studied 26 residents who were on call every other night. Each resident kept a sleep diary and underwent a battery of psychometric tests each morning for 18 or 19 days. The tests measured cognition, discernment, visual and auditory vigilance, and rapid eye-hand coordination. Sleep deprivation, defined as the lack of four hours of continuous sleep during the preceding 24 hours, occurred during 89 percent of the on-call nights, the authors report.

The tests showed that sleep deprivation did not affect overall cognitive or motor performance. "We conclude that the repetitive episodes of sleep deprivation associated with an every-other-night on-call schedule do not impair the performance of residents on psychometric tests and, by implication, performance in the provision of patient care," the authors write. "Criticism of traditional hospital on-call schedules should be based on objective data. The evidence available to date does not support arbitrary recommendations to limit working hours of residents."

JAMA September 23, 1988

REPORT: QUALITY OF CARE MUST BE DEFINED BEFORE IT CAN BE MEASURED

"Quality of care" in medicine cannot be assessed until there is agreement on what it consists of, concludes a report in *JAMA*. Unfortunately, the report acknowledges, such definitions, as well as agreement on them, are elusive.

"Before we attempt to assess the quality of care, either in general terms or in any particular site or situation, it is necessary to come to an agreement on what the elements that constitute it are," concludes the report by Avedis Donabedian, MD, MPH, of the University of Michigan School of Public Health, Ann Arbor. "To proceed to measurement without a firm foundation of prior agreement on what quality consists in is to court disaster."

"Those who have not experienced the intricacies of clinical practice demand measures that are easy, precise and complete," he writes. He admits that although "some elements in the quality of care are easy to define and measure... there are also profundities that still elude us."

The report identifies two elements essential in the assessment of quality in medicine: technical performance and interpersonal care. Technical performance is defined as, "the knowledge and judgment used in arriving at the appropriate strategies of care and on skill in implementing those strategies." Interpersonal care is defined as an exchange through which "the patient communicates information necessary for arriving at a diagnosis, as well as preferences necessary for selecting the most appropriate methods of care," the report says.

The author acknowledges that both elements offer abstract rather than finite measurements, further complicating the medical profession's efforts to provide a quality scale. To remedy this, Donabedian offers a three-part approach to quality assessment classified under the categories: structure, process and outcome.

"Structure" represents the setting under which care occurs, while "process" includes "the patient's activities in seeking care... as well as the practitioner's activities in making a diagnosis and recommending or implementing treatment." "Outcome" is the effect of care on the health of patients and the community.

"This three-part approach to quality assessment is possible only because good structure increases the likelihood of good process, and good process increases the likelihood of a good outcome," the author writes. Donabedian admits that his endeavor to provide a formula is not absolute and "it is equally clear that we have, as yet, much more to learn."

He reports that to perfect any measurement of quality, "we need to know a great deal more about the course of illness with and without alternative methods of care. To compare the consequences of these methods, we need to have more precise measure of the quality and quality of life," he says. In the end, "our information about the process and outcome of care needs to be more complete and accurate," he writes.

In an accompanying editorial, Dennis S. O'Leary, MD,

of the Joint Commission on Accreditation of Health care Organizations, Chicago, writes that "despite exhortations for self-examination from the physician community since early in this century, what we know and have done about quality assesment to date is remarkably little... Most important, physicians must assume a central role in managing the quality assessment process."

O'Leary calls for "a major effort to translate the theoretical framework (of Donabedian's formula) into an applied science. Ultimately, we will find that quality assessment, like the practice of medicine itself, is both science and art."

JAMA September 23, 1988

ALPHA-FETOPROTEIN TESTING FOR DOWN'S SYNDROME

An AMA science review panel, reporting in *JAMA*, calls maternal serum alpha-fetoprotein (AFP) measurement a safe mean of screening for Down's syndrome in pregnant women under age 35, but is not yet convinced of its effectiveness. Low levels of maternal serum AFP have been correlated with fetal chromosome abnormalities. Sixty-one percent of the 54-member AMA Diagnostic and Therapeutic Technology Assessment (DATTA) panel consider maternal serum AFP measurement safe for Down's screening, 26 percent call it investigational, 9 percent indeterminate. But only 23 percent of the panelists consider the test established as effective; 43 percent call it investigational and 26 percent indeterminate. Most panelists say "further refinement in the risk analysis and possibly the identification of other markers would be necessary before (maternal serum AFP testing) can become an effective screening tool for Down's syndrome," the report concludes.

JAMA September 23, 1988

ASSESSMENT OF LABORATORY QUALITY IN URINE DRUG TESTING

A report in *JAMA* describes a pilot study for proficiency testing of urine drug testing laboratories. The study, part of a program to develop accreditation guidelines for urine drug testing labs, involved 50 commercial labs on a voluntary basis, says the report by Kenneth H. Davis, of the Research Triangle Institute, Research Triangle Park, NC, and colleagues. Drug-free urine specimens were collected; these were then either "fortified" with commonly abused drugs or submitted unfortified to participating labs as "blanks." Samples were submitted on both a blind and "open" basis. Lab performance on open proficiency testing was comparable to that reported in existing proficiency testing programs, but blind testing "produced less accurate results in terms of apparent false-negatives," the authors say. However, they note, "significant difficulties were evident in carrying out blind testing and in comparing its results with those of open testing."

JAMA September 23, 1988

ACANTHAMOEBA KERATITIS

It has been four years since researchers first noted an association between contact lens wear and *Acanthamoeba* keratitis, a microorganism-caused corneal infection, and an editorial in September's *Archives of Ophthalmology* notes that the discovery "has single-handedly changed our approach to contact-lens associated keratitis and our recommendations regarding contact lens disinfection." This infection, one a curiosity, quickly became "the bane of corneal specialists across the country," writes Mary Beth Moore, MD, of Dallas, one of those to first report the problem. Once considered a rare infection due to trauma with a contaminated foreign body, early cases of *Acanthamoeba* keratitis in contact lens wearers were blamed on exposure to contaminated water from a hot tub, swimming pool or lake. Now it is known that careless lens handling—"any break in the contact lens care regimen that exposes the lens to a non-sterile environment contaminated with *Acanthamoeba*"—may lead to infection, Moore says. The number of cases of *Acanthamoeba* keratitis rose sharply between 1985 and 1987, probably due to increased awareness by clinicians and diagnostic improvements, as well as by increasing numbers of lens wearers mishandling their lenses. Drug treatment for this infections remains less than optimal (although another *Archives* report describes one promising new agent); prevention seems a more effective course, Moore says. Some patient mishandling of lenses is inevitable, she says, but "if we could eliminate all sources of contamination of the contact lens system, then perhaps we could eliminated 80 percent of cases."

MANAGING CANCER DURING PREGNANCY

Cancer is a leading cause of death in women of childbearing age, although its occurrence during pregnancy is uncommon. But when cancer does occur during pregnancy, treatment is difficult for patients, their families, and their physicians, notes a report in September's *Archivers of Internal Medicine*. When terminating the pregnancy is unacceptable, "decisions regarding the use of irradiation and chemotherapy are complicated by the well-known high risks of abortion and fetal malformation," says the review article, by Donald C. Doll of the Harry S. Truman Memorial Veterans Hospital and the University of Missouri Columbia, and colleagues. This risk, however, is concentrated in the first trimester and varies with the choice of anti-cancer agents; "there is only minimal evidence of increased risk of malformation or abortion in the second or third trimester," the authors report. Recent progress in cancer research has made cure a reasonable goal—even in some cases where initial treatment has been delayed or modified. Therefore, the authors conclude, in cases of cancer occurring during pregnancy, "when cure is a reasonable goal, curative therapy should not be compromised by modification or delay." But when treatment for cure or significant relief is not possible, "the goal should shift to protection of the fetus from damage by the injudicious use of teratogenic cancer therapy," they conclude.

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Use in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

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Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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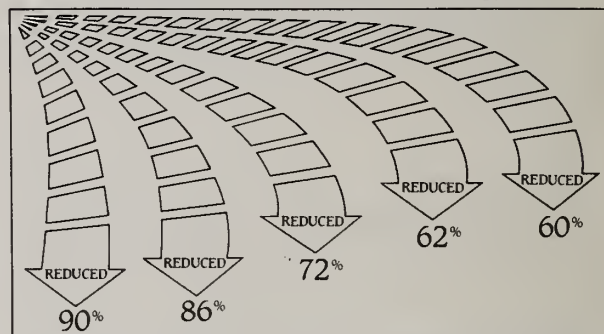
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VOL.80 - NUM. 12

DICIEMBRE 1988

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Publicación mensual, \$40.00 anuales. El Boletín se distribuye a todos los miembros de la Asociación Médica de Puerto Rico como parte de su cuota anual.

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Boletín de la Asociación Médica de Puerto Rico is published monthly for \$40.00 per year by Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, Santurce, P.R. 00908.

"POSTMASTER" Send address changes to Boletín Asociación Médica de Puerto Rico, 1305 Fernández Juncos Ave. P.O. Box 9387, Santurce, P.R. 00908.

Second Class postage paid at San Juan, P.R.

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Nuestra Portada

Adorna nuestra portada este mes un diseño original para tarjetas de Navidad de la artista puertorriqueña Myrna Baez.

La autora nació en Santurce, en agosto de 1931. Obtuvo un Bachillerato en Ciencias en la Universidad de Puerto Rico (1951), y la Maestría en Artes, en la Real Academia de San Fernando, de Madrid (1957). A su regreso a San Juan estudia en el Taller de Artes Gráficas del Instituto de Cultura, y más tarde, en 1969 asiste al Pratt Graphic Center.

Ha tenido exposiciones individuales en el Instituto de Cultura (1962), la Galería Colibrí, el Instituto Panameño de Artes (1966), el Museo de Ponce; la Universidad Interamericana, de San Germán; el Colegio Universitario del Sagrado Corazón (donde da clases); y la Galería Santiago (1974).

Ha participado en exposiciones colectivas en: Ateneo Puertorriqueño; Riverside Museum, Nueva York; Arte Actual de América y España (1963); Muestra Internacional de Grabado, Barcelona; Pratt Center (1970); Exp. Panamericana de Artes Gráficas, Cali (1972); Bienal del Grabado, Menton, Francia (1974); Bienal Gráfica, Florencia (1974) y las tres bienales de San Juan. En el Primer Salón de Pintura de la UNESCO, Museo de la Universidad (1974) obtuvo el Premio Unico.

Myrna Baez fue artista homenajeada en la VIII Bienal del Grabado Latinoamericano de San Juan en 1988. La Junta Editora agradece a la Dra. Lilliane Ferrer su valiosa colaboración para lograr la publicación de esta tarjeta navideña en nuestra portada. Asimismo agradece a la artista su gentileza al permitir la reproducción de su obra en nuestro Boletín.



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La Junta Editora del Boletín de la Asociación Médica de Puerto Rico reconoce la cooperación y apoyo brindado por una serie de personas para lograr la misión editorial encomendada.

Pocos de nuestros lectores y autores conocen la enorme contribución que hacen los arbitros al proceso de publicación de artículos en el Boletín. Estas personas desinteresadamente brindan su esfuerzo y su tiempo al análisis y corrección de los manuscritos sometidos para evaluación por esta Junta. También brindan valiosos servicios al Boletín con comentarios editoriales, artículos de repaso, material gráfico y otras tareas solicitadas por la Junta Editora para lograr confeccionar una publicación científica de calidad. Aprovechamos esta ocasión para expresar públicamente a estas personas nuestro agradecimiento por su valiosa labor durante todo este año.

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Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

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*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

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PRECAUTIONS

General: As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and very rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Quinolones may also cause anaphylactic reactions and cardiovascular collapse. Anaphylactic reactions may require epinephrine and other emergency measures.

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals. Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded. Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

Drug Interactions: Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin, resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

Probenecid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients: Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum concomitantly or within two hours after dosing. Ciprofloxacin may cause dizziness or lightheadedness; therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

- Salmonella/Microsome Test (Negative)
 - E. coli* DNA Repair Assay (Negative)
 - Mouse Lymphoma Cell Forward Mutation Assay (Positive)
 - Chinese Hamster V₇₉ Cell HGPRT Test (Negative)
 - Syrian Hamster Embryo Cell Transformation Assay (Negative)
 - Saccharomyces cerevisiae* Point Mutation Assay (Negative)
 - Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)
 - Rat Hepatocyte DNA Repair Assay (Positive)
- Thus, two of the eight tests were positive, but the following three *in vivo* test systems gave negative results:
- Rat Hepatocyte DNA Repair Assay
 - Microsome Test (Mice)
 - Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in animals have not yet been completed.

Pregnancy—Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

CONVENIENT B.I.D. DOSAGE

Recommended dosage schedule

Infection Site*	Severity of Infection	Dosage
Respiratory Tract*	Mild/Moderate	500 mg q12h
Bone and Joint*	Severe/Complicated	750 mg q12h
Skin/Skin Structure*	Severe/Complicated	750 mg q12h
Urinary Tract*	Mild/Moderate	250 mg q12h
	Severe/Complicated	500 mg q12h
Infectious Diarrhea*	Mild/Moderate/Severe	500 mg q12h

Nursing Mothers: It is not known whether ciprofloxacin is excreted in human milk, however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this, and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Ciprofloxacin should not be used in children because it causes arthropathy in immature animals (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%).

The most frequently reported events, drug related or not, were nausea [5.2%], diarrhea [2.3%], vomiting [2.0%], abdominal pain/discomfort [1.7%], headache [1.2%], restlessness [1.1%], and rash [1.1%]. Additional events that occurred in less than 1% of ciprofloxacin courses are listed below. Those typical of quinolones are italicized.

GASTROINTESTINAL: (See above), painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM: (See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.

SKIN/HYPERSENSITIVITY: (See above), pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported.

SPECIAL SENSES: blurred vision, disturbed vision, (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, bad taste.

MUSCULOSKELETAL: joint or back pain, joint stiffness, achiness, neck or chest pain, flare-up of gout.

RENAL/URIDGENITAL: interstitial nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR: palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY: epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship:

Hepatic—Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Hematologic—eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal—Elevations of Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. In the event of serious toxic reactions from overdosage, hemodialysis or peritoneal dialysis may aid in the removal of ciprofloxacin from the body, particularly if renal function is compromised.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro[®] (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and in Unit-Dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE INFORMATION).

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DERMATOLOGY DIAGNOSIS

Scott Ross, MD
Jorge L. Sánchez, MD

This is the case of a 16 year-old girl, referred to our department for management of several skin lesions. She described an asymptomatic white patch on her left forearm since birth. In addition, she also noted multiple slowly growing, firm, asymptomatic "pimples" at her face for the past four years. More recently, over the past year, she had noted growth of some thickened skin at the base of the nail of her second finger. She was in otherwise good health, with the exception of the seizure disorder since age two, which had been managed with diphenylhydantion (Dilantin®) 300mg daily. Her mother stated that she had had some difficulties with her school-work; she had repeated both the second and sixth grades. The mother denied knowledge of family members with similar skin lesions.

The physical examination showed a pleasant young woman with no signs of abnormality other than her skin lesions. On her face, she presented multiple brownish-red, 2-5mm, somewhat glistening papules localized to the naso-labial area and chin. A few additional papules were located on the cheeks and forehead. No pustular lesions were noted, though some lesions appeared excoriated. On her left forearm there was an oval-shaped, non-scaling hypopigmented patch, measuring 8 x 3.5cm. The index finger of her left hand presented firm, somewhat shiny and slightly tender, skin-colored, periungual papules measuring 6 x 4mm. The nail appeared normal. Heart, lungs, abdominal and neurologic exams were within normal limits.

The following laboratories were within normal limits: CBC, SMA-12, VDRL, dilantin levels and urinalysis.



Figure 1.



Figure 2.

WHAT IS YOUR DIAGNOSIS?

- (a) Acne vulgaris and Tinea versicolor
- (b) Tuberous sclerosis
- (c) Neurofibromatosis
- (d) Diphenylhydantoin hypersensitivity syndrome

Diagnosis: Tuberous sclerosis

Tuberous sclerosis is a complex neurocutaneous syndrome with autosomal dominant inheritance and a highly variable expressivity. Synonyms for the syndrome include Bourneville's disease (after a case description by Bourneville, in 1880) and epiloia, a term summarizing the classic triad of the syndrome, namely, epi for epilepsy, lo for low intelligence, and a for adenoma sebaceum. Lesions may be found in the skin, nervous system, heart, kidney and other organs due to a limited hyperplasia of ectodermal and mesodermal cells. The incidence of tuberous sclerosis is estimated to be 1 in 10,000 with sporadic cases identified in up to 75%. This suggests that there may be underidentified family members with minimal disease penetrance, rather than an extremely high spontaneous mutation rate. Its pathogenesis is unknown. The chromosomes appear morphologically unchanged, though apparently during embryologic development, the proliferative process involving precursor cell types becomes poorly controlled with locally excessive production of cells. Some degree of control is generally maintained and malignant transformation is rare.

Tuberous sclerosis may be present at birth, though most often the infant appears normal. The initial manifestation of the syndrome is often a seizure disorder or retarded psychomotor development. The facial lesions of adenoma sebaceum appear later in childhood, usually between the fourth and tenth years. There is a very wide spectrum of severity within the syndrome of tuberous sclerosis. Patients with severe neurologic dysfunction often have a relative paucity of skin findings and likewise, patients with prominent skin lesions may appear entirely normal neurologically.

The skin lesions of adenoma sebaceum are pathognomonic of tuberous sclerosis. They present at the face in over 90% of patients over four years of age with the disease. They represent angiofibromas with the sebaceous glands being only passively involved. The lesions typically present at the nasolabial folds, cheeks, chin and occasionally at the forehead and scalp as red to pink papules with a smooth, shiny surface (Fig. 1). They vary in size from 0.1 to about 1.0cm. Adenoma sebaceum may first be noted as a mild erythema in a "butterfly" distribution over the cheeks, intensified by crying. The lesions gradually increase in size but may grow rapidly at puberty. With time, the lesions may become verrucous or pedunculated, or may coalesce to form irregular plaques.

Approximately 85-95% of cases demonstrate congenital hypomelanotic macules which most often appear before any other skin lesions are noted. They are oval, in a linear orientation, with one end rounded and the other pointed, resembling the shape of an ash leaf (Fig. 2). These ash leaf macules are more easily demonstrated with a Wood's lamp, which emits light waves of 360nm. Selective absorption of light waves of this frequency by melanin provides relative enhancement of areas deficient in pigment. Electron microscopic studies have shown a normal number of melanocytes, though melanosomes have reduced amounts of pigment within the hypopigmented areas. Hypopigmentation may also be manifested

by confetti-like lesions, whitening of scalp hair and eyelash whitening.

On the trunk, the shagreen patch is a slightly elevated, flesh-colored area of skin with a leathery texture. The surface may resemble an orange peel ("peau d'orange") due to indentation by the cutaneous appendages. It may be seen in up to 70% of cases of tuberous sclerosis. These lesions occur most often at the lumbosacral region and consist of subepidermal fibrosis. They vary in size from 1 to 10cms in diameter.

In about half of the cases, the nail bed may show fibromatous changes with subungual fibromas (Koenen's tumors). They arise as small buds around the base of the nail or subungually, most often presenting after puberty (Fig. 2). They enlarge with time and may achieve large size and disrupt nail growth. In addition, gingival fibromas have also been noted.

Other lesions reported include multiple fibroepithelial polyps, early tooth pitting, café au lait macules, hemangiomas, pigmented nevi, lipomas, angiofibrolipomas and syringocystadenomas. None of these are pathognomonic for the disease.

As previously described, a prominent part of the presentation of tuberous sclerosis may involve infantile spasms and seizures. Patients may also demonstrate mental retardation. Foci of firm, broad, very white tissue among the cerebral convolutions represent areas of proliferation of glial tissue in the brain. These extend for several centimeters in the cerebral cortex, basal ganglia and ventricular walls, occurring in up to three-fourths of patients. These are the "tubers" after which the disease is named and are simulated by no other disease. They often calcify and will be visible on skull x-rays as "brain stones". Curvilinear calcifications may also be seen outlining the ventricles. Microscopically, these tubers most often presents interlacing rows of glial cells and plump fibrous astrocytes and may resemble astrocytoma. Gliomatous deposits may block the aqueduct or floor of the fourth ventricle producing an obstructive hydrocephalus. Retinal tumors, consisting of neuronal, glial and fibrous components may occur. Optic atrophy and cataracts have also been seen.

In addition to cutaneous and nervous system lesions, other organs are often involved in the disease process. Renal hamartomas have been reported in 60% of patients. They are usually multiple and bilateral and are uncommon before ten years of age. Most consist of connective tissue and blood vessel proliferations but epithelial cysts may be seen. In the adult, the usual clinical signs are flank pain associated with hematuria or pyuria. Rhabdomyoma of the heart, often multiple, have also been reported. Lung involvement with cysts formation is an uncommon finding. Bone manifestations are seen in as many as 85% of patients. Younger individuals show pseudocysts of the phalanges, while older patients have irregular or cortical thickening, especially of the metatarsal and metacarpal bones and the pelvis. The ribs may show sclerosis or irregular thickening of their lower margins. Hamartomas have been identified in the gastrointestinal tract, thyroid, larynx and testes and uterus. It seems likely that anomalies may occur in every organ.

Diagnosis is fairly easy when the triad of seizure disorder, mental deficiency, and characteristic skin lesions are present. However, early in the disease, or when the presentation is less typical, a careful search for additional clinical findings is required. In these cases, search for, and identification of the skin lesion is often rewarding in providing disease confirmation. Skull x-rays, CT scans and electroencephalograms identify the brain clacifications and tumor deposits. In addition, renal ultrasound and echocardiography may help identify renal and cardiac lesions.

Prevention is limited to counseling for affected individuals regarding chilbearing. No treatment is available to halt disease progression. Management is aimed at seizure control and the treatment of any lesions which achieve significance. Visceral lesions are often small and multiple and not amenable to surgical removal. Adenoma sebaceum may be removed by curettage and desiccation, freezing with liquid nitrogen, excision or dermabrasion. However, new lesions may and older lesions may continue to grow. Gingival and subungual fibromas may be similarly treated.

In the past, the prognosis relied on the ability to control the seizure disorder, with up to 85% not living beyond the age of 30. With better anticonvulsant therapy, the outcome now depends largely on the extent and location of visceral involvement. Patient with only skin lesions, probably have a normal life expectancy.

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Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

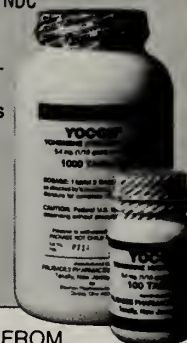
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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CLINICAL STUDIES

Benign Hyperglobulinemic Purpura of Waldenström: A Report of Seven Patients and Long-Term Follow-Up

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Summary: In 1943 Waldenström described three female patients with recurrent purpura of the lower limbs, hyperglobulinemia, and marked elevation of the sedimentation rate. Since then, 150 cases have been reported with this condition. A polyclonal gammopathy, high titers of rheumatoid factors and circulating immune complexes (IgG anti-IgG and IgA anti-IgG) have been found to be an integral part of this condition. A frequent association to collagen vascular disorders has been reported. Here we present our experience of 18 years with seven patients who fulfilled the diagnostic criteria of benign hyperglobulinemic purpura of Waldenström (BHPW). All the patients were female, and every one showed marked elevations of the sedimentation rate, high rheumatoid factor titers, a polyclonal gammopathy (IgG), and a fully normal coagulation work up. Three developed Sjögren's disease and two systemic lupus erythematosus.

A reevaluation of five available patients was performed (1988) which showed: skin biopsy with leukocytoclastic vasculitis, high levels of circulating immune complexes, and positive anti SS A antibodies. T lymphocyte subsets were abnormal suggesting an immunologic deregulation. Pathophysiology, diagnosis and treatment are discussed.

In 1943 Jan Waldenström¹ described in Sweden a group of patients with episodic purpura of the lower extremities, elevation of the sedimentation rate, and increased levels of gamma globulins in the serum. Since that initial report of three female patients, a number of similar cases have been described and reported by several authors. Practically, all reports point to the greater incidence in women and its close relationship to collagen disease.^{2, 3, 4, 5, 6, 7, 8}

The present report describes our experience at the University of Puerto Rico School of Medicine, with seven

patients who fulfilled the diagnostic criteria of benign hyperglobulinemic purpura of Waldenström (BHPW) as originally described. Five of these patients were diagnosed over 18 years ago, and three have been followed closely.

Material and Methods

The seven patients were referred to the University Hospital for evaluation of purpuric lesions. The history of recurrent purpura of the lower extremities, and the elevation of globulins on routine SMA-12, raised the suspicion of the diagnosis in the original patients.

Our first five patients underwent the following work-up: clinical history, physical examination, CBC, chest X-ray film, SMA-12, serum creatinine, urinalysis, platelet count, Ivy bleeding time, Lee White clotting time, one stage prothrombin time, kaolin activated partial thromboplastin time, 5M urea solubility test for factor XIII, RBC sedimentation rate, latex fixation test, antinuclear antibody detection by immunofluorescence, serum protein electrophoresis, and quantitative immunoglobulin analysis. Bone marrow aspiration was done in the original five patients. Biopsies of skin lesion were done to 4 patients.

The two new patients and three of the original patients had most of the above tests done. They also had complement levels C3/C4, Raji assay in reference laboratories, and T cell analysis by flow cytometry. All patients had SS A(Ro) antibody tests. The cell markers were done by flow cytometry according to routine methods using peripheral blood.⁹ The skin biopsies were stained with hematoxylin and eosin.

Clinical Features

All of our seven patients are women. The age of onset was less than thirty years in all but one patient, whose purpuras started at age fifty. The youngest was a patient whose lesions began to appear at age twelve.

Every patient showed recurrent crops of purpuric skin lesions circumscribed to the legs. These purpuras were always bilateral, most intense below the knees, but often reached up to the inguinal region. A sensation of burning

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Presented at the Annual Meeting of the American College of Physicians, Puerto Rico Chapter, September 1988, San Juan, Puerto Rico.

and/or pruritus usually preceded the actual purpuras. Prolonged standing or walking moderate distances, were described by all patients as the commonest precipitating factors. The skin lesions were not associated to trauma or accompanied by any other sort of bleeding manifestation. The episodes of leg purpuras have recurred over the years in every case.

The purpuras consisted of multiple papules (really palpable) of an erythematous-violaceous color. These papules were slightly indurated and ranged in size from 0.5 to 5 cms. Often, a tendency of the lesions to coalesce was observed. The purpuric nature of the papules was shown by the impossibility of blanching them with pressure. In some areas, delicate hemorrhagic vesicles or areas of erosion could be observed. (Figure 1)



Figure 1. Usual purpuric skin lesions of benign hyperglobulinemic purpura of Waldenström. These lesions are elevated, palpable, and do not blanch on pressure.

Laboratory Findings

Basic laboratory: The hemograms showed mild anemia and mild leukopenia in three patients. The urinalysis was normal in all patients, never suggesting a concomitant nephritis. The blood chemistries were equally normal in every instance, but for the elevation of serum globulins in all seven cases.

Coagulation studies: As shown in table II, no evidence of a coagulopathy was detected in any of our patients, in spite of the frequent and prominent purpuras. Platelet

aggregation studies done to several of the patients were also normal.

Plasma proteins: A most outstanding feature in every patient was the presence of a prominent, diffuse, wide based, gamma peak in the serum protein electrophoresis. (Figure 2) Quantitative immunoglobulin analysis disclosed that these polyclonal peaks were composed mostly of IgG. Cryoglobulins were not detected in any of the seven patients. Bone marrow studies in our patients showed modest mature plasmocytosis, always less than 10%.

Table I

Benign Hyperglobulinemic Purpura of Waldenström Clinical and Laboratory Findings on Initial Evaluation							
Patient	Sex	Age Years	Sed Rate mm/hr	Rheum* Factor	Hgb. gm/dl	WBC /cu mm	ANA
C.R.R.	F	12	51	Pos.	13.0	5400	Neg.
E.O.C.	F	20	50	Pos.	11.9	4100	Neg.
L.B.	F	21	44	Pos.	11.4	6400	Pos. 1:80
G.H.S.	F	26	48	Pos.	13.2	8100	Pos. 1:40
C.R.S.	F	29	47	Pos.	11.4	4700	Pos. 1:40
J.O.	F	30	52	Pos.	11.0	2500	Neg.
A.M.	F	50	35	Pos.	13.8	7900	Neg.

*All patients had titers of rheumatoid factor over 1:540

Table II

Coagulation Work Up				
Patient	Platelet Count /mm ³	Prothrombin Time seconds	P.T.T. seconds	Bleeding Time (Ivy) in min.
G.H.S.	220,000	12.4	42"	2' 30"
C.R.R.	245,000	14"	40"	4' 15"
C.R.S.	220,000	13"	30"	9'
J.O.	192,000	12"	35"	3'
E.O.C.	234,000	14"	40"	4'
A.M.	250,000	12.8"	23"	5'
L.B.	265,000	13"	30"	2' 20"

Table III

Benign Hyperglobulinemic Purpura of Waldenström Associated Diseases and Plasma Protein Disturbances on Initial Evaluation

Patient	Assoc. Diseases	Gamma Globulin n.v. 2.0-3.5 gm/dl	IgG n.v. 640-1430 mg/dl	IgA n.v. 60-460 mg/dl	Polyclonal Spike
C.R.R.	Sjögren's + SLE	4.2	3,800	220	Present
E.O.C.	Sjögren's	4.0	2,200	240	Present
L.B.	None	3.4	2,660	651	Present
G.H.S.	None	4.3	3,200	620	Present
C.R.S.	SLE	4.0	3,200	520	Present
J.O.	None	3.9	2,400	400	Present
A.M.	Sjögren's	1.9	1,500	200	Present

Table IV

Case	1988 Evaluation				
	C.R.R.	J.O.	A.M.	L.B.	G.H.S.
Associated Disease	SLE = Sjögren's	None	Sjögren's	None	None
Raji Cell	350	234	174	355	258
0-50 mcg/dl					
Anti Ro (SS A)	POS.	POS.	POS.	POS.	POS.
C 3	140	105.0	102.0	138.0	126.0
70-176 mg/dl					
C 4	12	16.0	21.0	12.0	14.0
12-36 mg/dl					
T4 Helper	31.0	30.4	68.9	42.1	27.6
27.6 nv 34-58 %					
T8 Supres.	17.0	8.5	12.0	15.7	26.1
26.1 nv 20-36 %					

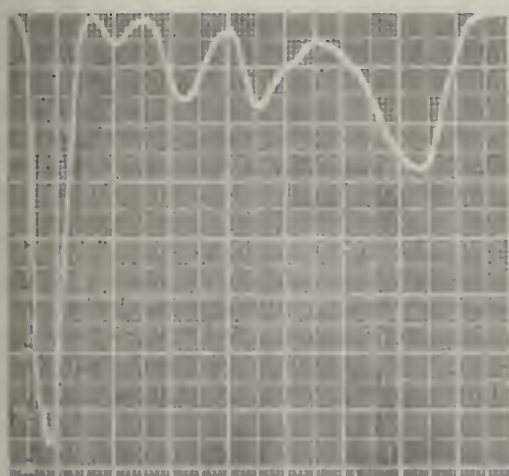


Figure 2. Serum protein electrophoresis of a patient with benign hyperglobulinemic purpura of Waldenström. Note the prominent polyclonal spike of the gamma region.

No evidence of multiple myeloma or of a similar plasma cell dyscrasia was detected.

Rheumatologic tests: A nuniversal finding was positivity for rheumatoid factor, with very high titers. Every case also showed marked elevation of the corrected sedimentation rate. ANA was positive transiently and with low titers in three patients. Two of them have eventually satisfied enough of the main criteria for the diagnosis of SLE. C3 and C4 complement levels were normal in every patient. All of the five tested patients were positive for autoantibodies to SS-A(Ro). The same five cases showed distinctly the presence of circulating immune complexes by the Raji cell method.

Cell Mediated Immunity

The phenotyping of lymphocytes performed to five of our patients, revealed significant decrease of the T8-suppressor subset in four of them. The T8-helper subset was normal or elevated in all.

Association to collagenosis

Upon long term follow up, two of our original five patients developed xerostomia, keratoconjunctivitis sicca, arthritis, and positive lip biopsy to establish the diagnosis of Sjögren's syndrome. One of the two new patients showed sicca syndrome and arthritis, most consistent with Sjögren's syndrome, increasing to three the patients with such condition. Two of our patients developed enough diagnostic criteria for SLE; one of them also had Sjögren's.

Skin biopsies

Skin biopsies were done to four of our patients. See figure 3. They all showed leukocytoclastic vasculitis. The main changes were in the small vessels of the dermis. The venules showed swelling of the endothelial walls, and deposits of fibrinoid material around them. A severe inflammatory reaction was present, specially around the capillaries, composed mostly of neutrophils. Many of the latter showed fragmentation of nuclei, a feature characteristic of leukocytoclastic vasculitis.

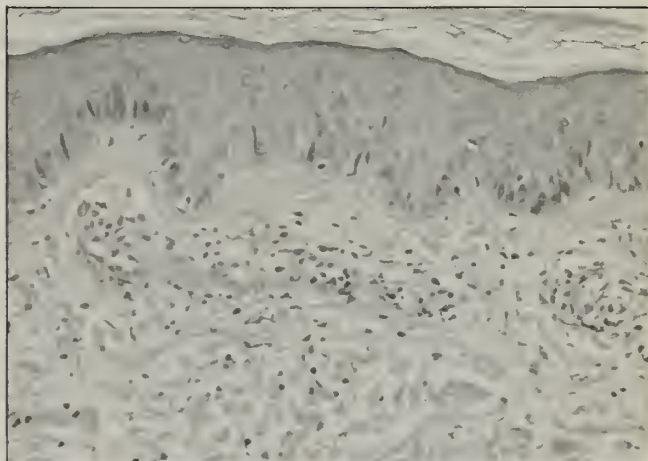


Figure 3. Skin biopsy of a palpable purpuric lesion of benign hyperglobulinemic purpura of Waldenström. The changes are those of a leukocytoclastic vasculitis.

Discussion

Bening hyperglobulinemic purpura as originally described by Waldenström, consisted of recurrent purpuras in the lower extremities, of young women elevated sedimentation rate, and increased levels of immunoglobulins in the serum.¹ Following the initial report, close to 150 patients have been presented in the literature. Those have consistently shown a high frequency in young women, a close association to collagen vascular disorders, and absence of altered coagulation processes.^{2, 3, 4, 5, 6, 7, 11, 13, 14}

The findings in our group of patients are in accordance to those reported by others.⁸ These palpable purpuras are more frequent in the lower extremities, and are generally precipitated by prolonged standing or walking. The lesions are usually preceded by pruritus or a prickly sensation. Chronicity is a hallmark of this condition, and after a number of episodes the accumulation of hemosi-

derin causes areas of brownish discoloration in the lower extremities. Thus it is fairly common to observe fresh purpuric lesions superimposed over areas of old hemosiderin deposits. No problems with platelets or clotting factors have been described in this disorder.

The laboratory findings of elevated sedimentation rate, positive latex fixation for rheumatoid factor, and increased levels of IgG forming a diffuse polyclonal peak in the serum protein electrophoresis, are consistently present both in the BHPW cases in the literature and in our patients.¹² Mild anemia and modest leukopenia have been described in BHPW, and three of our patients showed those findings.

Dermatopathology

The cutaneous lesions of BHPW are palpable purpuras which histologically show damage to the cutaneous vessels and infiltration by neutrophils showing fragmentation of nuclei (leukocytoclasia). This leukocytoclastic vasculitis is limited to the small blood vessels of the dermis, which show swelling of their endothelial cells and deposits of strongly eosinophilic strands of fibrin within and around their walls. These deposits of fibrin are accompanied by marked edema in the wall of the blood vessels. Such combination give a smudgy appearance to the walls and perivascular collagen referred to as fibrinoid degeneration.

Association with collagenosis

There is a close association of BHPW with collagen vascular disorders, specially with Sjögren's syndrome and systemic lupus erythematosus. In a series of twenty four patients with BHPW, Kyle⁸ reported three with Sjögren's syndrome, four with keratoconjunctivitis sicca, and four with SLE. In our group of seven patients, three have Sjögren's syndrome and two have enough criteriae for the diagnosis of SLE. One of the cases has both conditions.

Sjögren's syndrome patients show up to 85% incidence of anti SS-B(La) antibodies and a much lower number (13%) of them, have anti SS-A(Ro) antibodies.^{17, 18} In Sjögren's a very close association of the presence of antibodies against SS-A(Ro) with systemic manifestations is known to exist. Of the latter the most prominent are: purpuras, vasculitis, anemia, leukopenia, hyperglobulinemia, and elevated rheumatoid factor titers. In our series, most of the above manifestations are present, and all of the five tested patients were positive for anti-SS-A(Ro) autoantibodies, three of them without Sjögren's.¹⁰

Around 45% of SLE patients have antibodies to SS-A(Ro), often in combination with anti SS-B(La). SLE, Sjögren's, and the presence of anti SS-A(Ro)/anti SS-B(La) antibodies are associated to a higher frequency of HLA-DR2 and HLA-DR3. The fact that all of our tested cases have anti-SS A(Ro) antibodies puts BHPW even closer to Sjögren's and SLE. So it would be interesting to learn the frequency of the above mentioned transplant antigens in BHPW.

Pathophysiology

The pathophysiologic mechanism that mediates the purpuras has not been fully elucidated, but the role of an antigen antibody complex as the cause of the vasculitis, has been strongly suggested.^{15, 16} A leukocytoclastic vasculitis secondary to immune complex deposition is most likely the basic lesion. The presence of circulating immune complexes was clearly shown in our patients by the Raji cell method. In recent years the consistent presence of circulating immune complexes has been an essential feature of BHPW. Those complexes are usually composed by IgG-anti-IgG or IgA-anti-IgG. This explains the universal positive rheumatoid factor in our patients. There is good evidence favoring that the immune complexes can migrate into the vessel walls causing an Arthus type (complement mediated) of hypersensitivity vasculitis. Such is followed by an acute inflammatory reaction with red cell extravasation which is later phagocytized, producing local hemosiderosis. Given that the lesions are limited to the lower limbs and precipitated by prolonged standing, increased hydrostatic pressure seems to play a role, probably facilitating the deposition of immune complexes.

Why these patients develop circulating immune complexes is nowadays a subject of speculation. Studies of lymphocyte subsets in RA and SLE show a decreased T8 suppressor population, with a normal or increased T4 helper subset. Lymphocyte phenotyping in five of our patients shows abnormally low T8 suppressor cells in four cases. Of those, only one has SLE. Such findings are in agreement with the BHPW theory of Ferreiro¹⁴ of an immunoregulatory defect. According to it, an endogenous antigen induces polyclonal activation of B lymphocytes with the production of immune complexes. The decreased T8 population fails to properly inhibit such activation, resulting in a hyperactivated polyclonal population of B lymphocytes, with uncontrolled production of immunoglobulins.

Therapy

Except for the cosmetic aspect and the local discomfort, BHPW is a condition of little impact in the patients' health. Nevertheless, its close association to Sjögren's and systemic lupus, and occasionally to multiple myeloma and lymphoma, makes medical follow up a necessity.

Various therapeutic trials with corticosteroids, 6-thioguanine, azathioprine, and other immunosuppressive drugs, have failed to bring a clearcut or lasting improvement of the purpuras. Plasmapheresis in one of our patients induced an excellent, yet transient improvement. Such benefit has been reported in other patients,¹⁹ but it is a treatment of poor cost effectiveness for an essentially benign condition. So the treatment of BHPW consists mainly of: leg elevation, use of elastic stockings, avoidance of prolonged standing and in more severe cases, Jobst pressure gradient stockings.

In essence BHPW is a condition that must be considered in the differential diagnosis of young females presenting with purpuric lesions of the lower extremities. A normal coagulation work up, an elevated sedimenta-

tion rate, a very positive rheumatoid factor and a polyclonal gammopathy are consistent findings. Although an essentially benign condition, the clinician should be alert to the appearance of manifestations suggestive of collagenosis or malignancy (multiple myeloma and lymphoma have been reported in association to BHPW), which may need specific therapy.²⁰

Resumen: Desde el reporte original (1943), se han descrito 150 casos de la púrpura hiperglobulinémica de Waldenström. Dicha condición se caracteriza por la recurrencia de lesiones purpúricas en las extremidades inferiores de mujeres jóvenes. Concomitantemente en estos pacientes se encuentra: prolongación sustancial del tiempo de sedimentación de los hematíes, altos niveles de factor reumatoideo, marcado aumento de las inmunoglobulinas, complejos de antígeno-anticuerpo circulantes y pruebas de coagulación sanguínea normales. Se ha descrito una alta coincidencia con las collagenosis.

Aquí presentamos nuestra experiencia de 18 años con 7 pacientes con este diagnóstico. Todos los pacientes son mujeres, con comienzo de su mal a una edad joven. Sus pruebas de coagulación fueron normales, la velocidad de sedimentación de hematíes fue uniformemente alta, las inmunoglobulinas (especialmente IgG) mostraron aumento significativo y la elevación del factor reumatoideo fue notable en todas. Tres pacientes presentaron enfermedad de Sjögren, y dos lupus sistémico.

Se hizo reevaluación en 1988 a cinco pacientes disponibles, la cual reveló: biopsias de piel con vasculitis leucocitoclástica, complejos antígeno-anticuerpo circulantes y positividad para anticuerpos contra SS A en todos los casos. Los estudios de linfocitos T fueron anormales y sugieren un problema en el balance inmunológico de estos pacientes. Se discute la patofisiología y el tratamiento.

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Rectal Myectomy in the Management of Short Segment Hirschsprung's Disease

Victor N. Ortiz, MD
José Cebollero, MD

Summary: Aganglionosis should be suspected in children with a clinical presentation of constipation refractory to medical therapy. The technique of rectal suction biopsy is not only a simple and accurate method to establish this diagnosis but also can be used in mapping to determine the length of affected bowel.

In short segment Hirschsprung's Disease, posterior anorectal myectomy seems to be the best surgical alternative. In our experience besides being associated with no significant morbidity or mortality it represented clinical improvement or cure to 87% of the patients so treated.

Hirschsprung's disease can be classified as long segment, classic (rectosigmoid), and short segment types. Traditionally, Hirschsprung's disease has been surgically managed by the performance of a pull-through procedure with its low mortality, but significant morbidity. We plan to present our experience in the management of short segment Hirschsprung's disease with special emphasis on its surgical management by rectal myectomy.

In a review of 501 cases of Hirschsprung's disease that Dr. Swenson collected over 26 years there was an incidence of 7.5% of all cases that could be described as short segment.¹ Dr. Hugh B. Lynn, two years later, from the Mayo Clinic experience described an incidence of 37%.² Although there is a wide variation in the overall incidence of short segment Hirschsprung's disease, there is a definite trend towards a higher incidence of reported cases of this disease entity. This can be attributed to an increase awareness of the condition and referral for investigation of patients, who have been attending Pediatric Clinics for many years with the diagnosis of constipation. It is the purpose of this series to corroborate that the incidence of short segment Hirschsprung's disease is much higher than it is claimed to be, and that it can be managed safely by anorectal myectomy.

Materials and Methods

Fifteen out of 135 children referred with refractory constipation to the Pediatric Surgery Division of the Department of Surgery at the Mayagüez Medical Center during the period of July 1983 through December 1984, were diagnosed as having short segment Hirschsprung's disease, (11 percent).

Barium enema was performed in all patients. There was a male to female ratio of 9 to 6. Mean age at operation was 4.4 years. Final diagnosis was made by rectal suction biopsy.

Myectomy Technique

The procedure to be described is a modification of previously reported techniques.^{3, 4} All myectomies were performed by the same surgical team. Cleansing normal saline enemas were given the day before surgery. With the patient in a modified Frogs-lithotomy position, under general endotracheal anesthesia with muscle relaxants, the anus is stretched and five stay retracting sutures applied. A transverse mucosal incision is made approximately one cm from the dentate line (Figure 1). The mucosa is then separated from the muscular layer by blunt dissection and the muscle grasped with Pennington forceps. A strip of muscle one cm wide is cranially removed for varying distances (Figure 2). In our series the length of the myectomy averaged six cms. The puborectalis muscle is identified and preserved. The specimen is then carefully placed in a sterile tongue blade and kept in place with #25 gauge needles. Care is taken in identifying the cranial and caudal ends. The specimen is placed in formalin and sent to the pathology laboratory for microscopic interpretation.

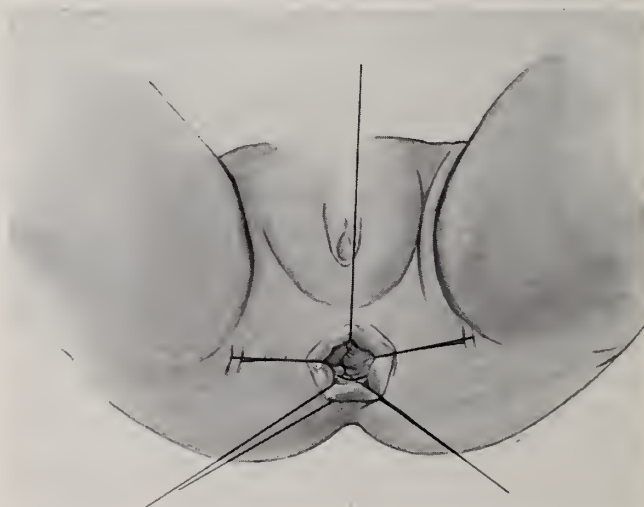


Figure 1. Anus stretched with stay retracting sutures. A transverse mucosal incision is made 1 cm from the dentate line.

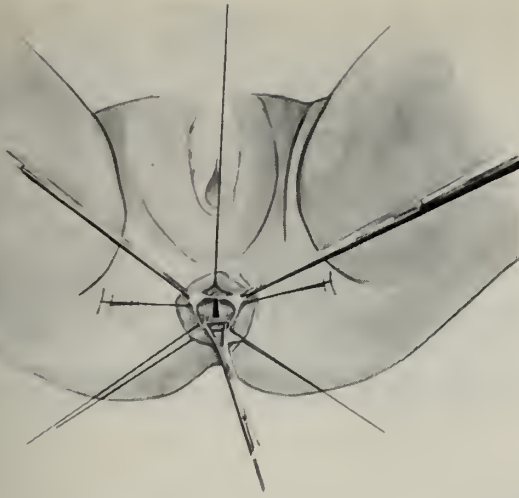


Figure 2. Mucosa is separated from the muscular layer. A one cm wide strip of muscle is cranially removed for varying distances.

The presacral space is drained with a small Penrose drain and this brought out through a stab wound in the perineal skin, posterior to the anus. The mucosal incision is approximated with 4-0 polyglycolic acid sutures. The children are given stool softeners postoperatively and the drain is removed after the first bowel movement.

Two main groups, according to presence (Group I) or absence (Group II) of ganglion cells at the upper end of the myectomy specimen, were identified. There were ten patients in the first group and five patients in the second group. Patients were followed for a minimum of 12 months after myectomy and their clinical status categorized as:

- a) Excellent: normal bowel habits
- b) Improved: normal bowel habits, but laxatives required intermittently
- c) No real change

Results

There was no postoperative morbidity or mortality. Of the ten patients in group I, nine had excellent results and one was improved. Of the five patients in group II, one patient had excellent results, one patient was improved and three required further surgical management. The clinical outcome of this subgroup was as follows: two patients required pull-through procedure, and the other required a second myectomy, this time with histological demonstration of ganglion cells at the cephalad end and clinically cured.

Therefore, of the 15 patients managed by rectal myectomy 11 had ganglion cells present at the upper end; ten of these are cured and one is improved.

In the second group, where no ganglion cells were found at the upper end, (four patients) one patient is cured, one is improved, and two are considered failures of the myectomy procedure. The difference between the results obtained in the two groups is significant to P less than 0.1 by the Students T test.

Discussion

Short segment Hirschsprung's disease is probably more common than generally stated. In our series during the period studied it represented 33 percent of the patients with Hirschsprung's disease who were surgically treated.

Patients with constipation, who do not have the classical abdominal distention, the explosive response to either enemas or rectal examination, or who pass through the early months of life without major difficulties are usually assumed not to have Hirschsprung's disease. If the patient is female, it is considered less likely that the difficulties are due to aganglionosis, since the ratio of male to female in Hirschsprung's is approximately 9:1.

In our series, the male to female ratio was 9 to 4 which is similar to the reported ratio of 2 to 1 for short segment aganglionosis, reported in the literature.

Moreover, roentgenographic studies on these patients may not be diagnostic since no transition zone is usually found. A 24 hours post evaluation film should be requested always since fecal retention and findings of megarectum, may give the clue to diagnosis. Although fecal retention at 24 hours is an almost universal roentgenographic findings, megarectum is not always found.

In older children, the presence of fecal soiling has been considered traditionally an indication of emotional difficulties. Psychiatric counseling and protracted management with enemas and laxatives are recommended without any attempt to rule out aganglionosis. A prompt rectal suction biopsy will eliminate this problem without submitting these patients to general anesthesia. We used the Quinton multi-purpose biopsy tube for the performance of the rectal suction biopsies.

In our series, patients in whom ganglion cells were identified at the upper end of the myectomy specimen were completely cured or markedly improved at the end of the time period under study. The clinical outcome of patients in whom no ganglion cells were present at the upper end of the myectomy specimen was unsatisfactory, as two out of four required pull-through procedures.

In order to explain those two patients with no ganglion cells at the upper myectomy specimen and who were clinically cured or markedly improved, we can assume that the myectomy ended close to the region of normal ganglionosis, thus reducing the resistance produced by the very short remaining aganglionic segment.

Anorectal dilatation under anesthesia might give temporary improvement, but any change should regress within six months. Therefore, the improvement noted in our patients, followed for not less than 12 months must be attributed to the myectomy procedure. All rectal suction biopsies should be obtained 4 cm. from than anal verge, thus avoiding any area of possible hypoganglionosis or false positive results.⁵

In many instances mapping of the rectum can be carried out by obtaining rectal suction biopsies every two cm. proximally until ganglion cells are obtained, thus delimiting the length of the aganglionic segment.

If we take into consideration that out of the 15 patients histologically proved to have Hirschsprung's disease only

two required pull-through procedures we can safely conclude that rectal myectomy has a place in the treatment of patients with Hirschsprung's disease of the short segment type.

All efforts should be made to identify and separate short segment Hirschsprung's disease from the classical type, since its management by anorectal myectomy carries a low morbidity and mortality, when compared to the more complex pull-through procedures.

Resumen: El diagnóstico de aganglionosis debe ser sospechado en todo niño que se presenta con estreñimiento, refractario a tratamiento médico. La técnica de biopsia rectal por succión es un método simple, y exacto que no solamente establece el diagnóstico de Hirschsprung's sino también el largo del segmento agangliónico.

En el Hirschsprung de segmento corto la técnica de miectomía anorectal es la mejor alternativa terapéutica. En nuestra experiencia ésta estuvo asociada con morbilidad y mortalidad no significativa y representó mejoría clínica en un 87 por ciento de los pacientes tratados.

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VIII SCIENTIFIC MEETING INTER-AMERICAN SOCIETY OF HYPERTENSION



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Notification of Abstract acceptance January 30, 1989
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ARTICULOS ESPECIALES

Daño Cerebral y El Obstetra

Antonio Morales Pereira, MD, FACOG

Desde que en 1862, John Little¹ postulara que la perlesía cerebral era consecuencia de eventos ocurridos durante el parto o el alumbramiento, el obstetra ha cargado con la culpa en estos casos. Aunque Sigmund Freud² luego en 1897 expuso que el evento anómalo del parto podría ser consecuencia y no la causa, y que ésta pudiera encontrarse en el período prenatal, Little, que era un cirujano ortopédico, estaba convencido que la causa no era otra que el proceso del parto. Esta creencia perduró por más de un siglo, hasta los años setenta cuando empiezan a salir estudios que indicaban que la hipótesis de Little no era del todo correcta. Aún para los años cincuenta y sesenta, la mayoría de los escritos reflejaban la opinión de que los insultos perinatales eran predominantemente responsables del daño neurológico en los neonatos.³ Esta opinión aun permea en el pensamiento clínico de algunos y favorece a los demandantes en los litigios en corte, cuando se reclama daño cerebral. Tanto es así, que el estado de Virginia ha pasado una ley para compensar a todo niño que desarrolle daño cerebral u otro daño neurológico, sea éste o no, consecuencia del parto.

Los adelantos técnicos introducidos de 1960 en adelante, que nos permiten dar un mejor cuidado prenatal y de parto, no han reducido significativamente la incidencia de perlesía cerebral.⁴ Ni la amniocentesis, la sonografía, el monitoreo fetal electrónico, los estudios de gases arteriales, ni aun el incremento en el número de cesáreas han podido reducir el número de niños con ésta condición. Hoy en día hay un consenso entre los investigadores, basándose en estudios epidemiológicos y experimentación en monos que los eventos asociados al parto no son la causa común de perlesía cerebral.⁵ También hay una opinión generalizada de que en casos individuales la causa es frecuentemente desconocida. Nelson y Ellenberg,⁶ dos investigadores asociados a los Institutos Nacionales de Salud y Enfermedades Neurológicas, son posiblemente los que más han estudiado esta materia. Ellos opinan que en la mayoría de los casos de perlesía cerebral, la etiología permanece inexplicada. No se puede negar que hay casos de daño cerebral asociado o que surgen de eventos acontecidos en el parto, pero en estos casos hay cambios que deben ocurrir concomitantemente.

En casos en que claramente ocurren episodios de anoxia prolongada durante el parto, el recién nacido nace deprimido, requiere resuscitación, se hallará acidótico y tendrá eritrocitos nucleados en sangre.^{7, 8}

Todos estos cambios pueden proveer evidencia de que hubo asfixia intra-uterina.⁸ Sin embargo cuando hay asfixia severa y prolongada en el parto, no solamente habrá daño cerebral sino que también debe haber evidencia de daño en otros órganos tales como hígado, riñón, sistema cardiovascular y pulmón, además de los cambios arriba descritos. El feto que sufre el insulto anóxico durante el parto, se debe aclarar, puede estar evidenciando ese insulto hipóxico porque ya estaba afectado de antemano y simplemente esa hipoxia es el reflejo de su afectación crónica que data de mucho antes del parto. Desafortunadamente, las técnicas que tenemos a mano no son lo suficientemente sofisticadas para que nos permitan detectar todos los fetos que puedan estar a riesgo. Por medio de sonografía podemos detectar aquel con anomalías congénitas, el que tiene oligodramnios, el que aparece hipotónico, el atrasado en su crecimiento y el que respira infrecuentemente. Por medio de pruebas con monitor fetal podemos identificar aquel que tiene insuficiencia placentaria, pero no podemos detectar a todo feto en estrés hipóxico crónico.⁹

Por otro lado, la condición de perlesía cerebral no está precedida siempre por evidencia de asfixia intrauterina. De hecho, 75% de los niños que desarrollan perlesía cerebral nacen con una puntuación Apgar normal y la gran mayoría de los que nacen con un Apgar bajo, subsiguientemente se encuentran con un sistema nervioso central intacto.¹⁰⁻¹¹ La puntuación de Apgar por sí sola no puede establecer si hubo suficiente grado de hipoxia para causar perlesía cerebral. Un niño con un Apgar de 0-3 a los 5 minutos, que mejora a 4 o mejor de 4, tiene un 99% de oportunidad de no desarrollar perlesía cerebral para la edad de 7 años.¹² El Colegio Americano de Obstetras y Ginecólogos (ACOG) y la Academia Americana de Pediatría (AAP) en una opinión de su comité conjunto de Medicina Materno-Fetal en noviembre de 1986 han expresado lo siguiente: la correlación de la puntuación de Apgar con daño neurológico posterior, aumenta cuando la puntuación es 0-3 a los 10, 15 y 20 minutos.¹³ Aunque la asfixia cerebral puede ser breve o transitoria y aunque se pueda manifestar con un Apgar bajo a los 5 minutos, hipoxia substancial causante de perlesía cerebral puede presumirse solamente cuando los

siguientes criterios están presentes:

1. El Apgar es de 0-3 a los 10 minutos (en ausencia de otras causas).
2. El infante permanece hipotónico por lo menos varias horas.¹⁴
3. El infante desarrolla convulsiones.¹⁵

En otras palabras que el Apgar no puede usarse como pronosticador de daño cerebral, por lo menos al minuto ni a los 5 minutos. En un niño que desarrolla perlesía cerebral, una puntuación baja de Apgar al minuto y a los cinco minutos, provee evidencia insuficiente de que el daño fue debido a hipoxia.

Myers, uno de los escritores e investigadores más prolíficos en el área de privación de oxígeno con daño neurológico subsiguiente, ha expresado que: Cuando se considera que la asfixia debe ser severa y que la duración de ésta debe ser prolongada para que se produzca daño cerebral, es aparente que el sobrevivir con este daño es relativamente raro y la muerte o salir neurológicamente intacto es el resultado más común.¹⁶ Niswander,¹⁷ siguiendo el concepto de Myers ha sugerido que para que ocurra daño cerebral asociado a asfixia perinatal, es necesario que haya shock, con disminución de circulación al cerebro, acidemia, y daño a otros órganos como apuntáramos antes. La asfixia tiene que ser severa pues el organismo trata de seguir supliendo oxígeno al cerebro a expensas de otros órganos. Tomando en consideración los estudios de Myers, Niswander, Sarnat, Brann¹⁸ y otros, podemos describir el cuadro típico que veremos cuando ocurre una asfixia severa y prolongada: tendremos un neonato con algún grado de shock, a tal extremo que requerirá resucitación. Exhibirá flacidez en 4-12 horas, tendrá aumento en presión intra-craniana como resultado de edema cerebral. Desarrollará convulsiones leves y cortas dentro de doce horas, pero éstas se tornarán en severas y generalizadas. Se notarán cambios isquémicos en los intestinos, pulmones y corazón y morirá por fallo respiratorio o cardíaco en varios días. Aunque en el humano no es posible medir el grado de asfixia como en el mono, se cree que ocurren cambios similares.

Para que en el neonato humano podamos asociar un daño neurológico con asfixia intra-parto, debemos tener un cuadro como el de arriba descrito. Clínicamente, el pediatra notará que las convulsiones, que deben desarrollarse dentro de las primeras 24-48 horas de vida, son sumamente difícil de controlar y se tornan del tipo gran mal. Las fontanelas se abultarán debido al edema cerebral o por compresión de los ventrículos y así deben aparecer en la tomografía computarizada (CAT-scan) o por resonancia magnética.¹⁹ Aun así, el hecho de que el cuadro arriba descrito suceda, el evento hipóxico no puede atribuirse a negligencia ni a trauma obstétrico durante el parto. Como expresamos anteriormente la etiología de perlesía cerebral es desconocida en la inmensa mayoría de los casos. La asfixia intra-uterina repitiendo, puede ser el resultado de daño cerebral crónico previo al parto y puede ser señal de ese daño y no la causa. Si el curso clínico del neonato no sigue el típico descrito por Myers, se debe buscar otras causas. Entre las posibilidades se deben perseguir causas genéticas (rasgos físicos dismórficos, una cabeza pequeña en circunferen-

cia), patología umbilical, cordón muy corto o muy largo, evidencia de infección intra-uterina, (retardación de crecimiento físico simétrico), un hematocrito excesivamente alto o evidencia en la placenta de una endovasculitis hemorrágica. El envío de la placenta y cordón umbilical al patólogo para examen microscópico, tomografía computarizada del cráneo y medición de pH y gases en la sangre del cordón umbilical, son pasos que el obstetra debe tomar en unión al pediatra o neonatólogo en caso que se sospeche daño cerebral de cualquier tipo. En casos en que el bebé nazca bañado en meconio en algún grado, se debe enviar la placenta, pues si el meconio estaba presente antes del parto se verá en los macrófagos de estos tejidos. Otras condiciones, de acuerdo a Nelson y Ellenberg, que pueden asociarse a daño cerebral son: disfunción tiroidea, "fetal stroke", infecciones virales intrauterinas, otros defectos congénitos no-neurológicos, retardación mental en la madre, uso de estrógenos durante el embarazo y otros.²⁰

El uso del alcohol, tabaco y otras drogas pueden tener influencias nocivas en el feto en el período pre-natal.²¹ El abuso de estas drogas se debe documentar en el expediente prenatal.

¿Qué significa toda esta data? A lo que se traduce es que el obstetra que por muchos años se le responsabilizó por el desarrollo de perlesía cerebral en neonatos que él atendía, ve ahora que esa atribución era injusta. Por lo tanto, ahora el obstetra que se encuentre en situaciones en que nace un bebé deprimido o con evidencia de déficit neurológico, debe determinar primeramente, si ocurrió un evento intra-parto que pudo haber causado la condición, luego, determinar si hubo cuidado obstétrico inadecuado. Si no hubo, el próximo paso debe ser trazar señales de eventos prenatales que puedan haber influenciado el desarrollo del feto.

El manejo de riesgos para un obstetra se ha tornado en un punto muy crucial en el cuidado de la embarazada. Esperamos que los obstetras de Puerto Rico estén al tanto de todos estos nuevos hallazgos, que documenten que su paciente embarazada recibió un cuidado profesionalmente adecuado, que demostró interés, sensibilidad y calor humano en su cuidado. Luego, si el daño neurológico no está ligado al parto o al cuidado rendido, buscar factores que puedan haber afectado el resultado final. Indudablemente el último capítulo sobre perlesía cerebral no se ha escrito. El estudio de Freeman, publicado por los Institutos Nacionales de Salud en abril de 1985, ha venido a aclarar un poco la confusión y a reivindicar en parte al obstetra. Es imprescindible que además de educarnos, hagamos lo propio con los abogados y los jueces en esta materia, pues no es justo que sigamos siendo inculcados en las cortes por algo que estuvo fuera de nuestro control. El obstetra no debe temer en casos de daño neurológico, siempre y cuando haya brindado un cuidado de excelencia en el prenatal y el parto y pueda demostrarlo en el expediente. Cualquier paso terapéutico o de intervención debe seguir las normas y procedimientos de rigor a la luz de los estándares aceptados, tomando en consideración los métodos modernos de comunicación y actuando como actuaría un obstetra competente, justo y razonable, en la misma situación.

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Realities of the Cardiovascular Center

Enrique Vázquez-Quintana, MD, FACS*

In May 30, 1986 our governor signed law 51 creating the Cardiovascular Center for Puerto Rico and the Caribbean. One year later, a corner stone ceremony was held in the place where the Center will be located.

It is interesting to note that the legislation by means of which the Cardiovascular Center for Puerto Rico and the Caribbean was enacted by non-surgeons and with no participation of cardiovascular or general surgeons. It is widely known that surgeons are the professionals more actively involved and affected by the functioning of the Puerto Rico Medical Center. In general the internists and administrators of the University Hospital are not directly involved in the day to day functioning or policy decisions made at the Puerto Rico Medical Center. Interestingly the Cardiovascular Center law is a typical escape from the Puerto Rico Medical Center, from its problems. This fact clearly demonstrates that even the non-surgeons are dissatisfied with the functioning of the existing Medical Center and as a result they have proposed the creation of a new public corporation, totally independent from the Puerto Rico Medical Center. It reminds me of the movie "Escape from New York."

The creation of the Puerto Rico Medical Center was based on the economy of scales, it has been demonstrated that as institutions grow larger, inefficiency and expenses increase. The Medical Center has proven to be more expensive than anticipated, and the main objective set at its inception has not materialized. In fact some of the participating institutions have established independent units such as x-rays, laboratory and operating rooms and have decreased the purchasing of services from the Central Building.

Very few people know the actual functioning of the Puerto Rico Medical Center, in particular our legislators, may not be aware or simply do not know the intricacies of the Puerto Rico Medical Center and its relationship with the participating institutions. It was much simpler to avoid dealing with the inefficient and expensive Medical Center by creating a new entity in a new building to be known as the Cardiovascular Center for Puerto Rico and the Caribbean. Unfortunately there is no guarantee that the Cardiovascular Center will be economically self-sufficient.

Two private hospitals have requested and obtained authorization to operate as cardiovascular centers. These institutions are already functioning as hospitals and can readily start providing cardiovascular services to their patients, on the other hand the Puerto Rico Cardiovascular Center is in the stage of breaking the ground. Evidently the Puerto Rico Cardiovascular Center will be competing with the private institutions for the same patient population. I suspect that the private patients will continue to have their cardiovascular procedures done in private hospitals either in Puerto Rico or in the United States and our Cardiovascular Center will continue to receive and treat the indigent population. The only way to deal with this dichotomy is to sustain the original position of our government in having only one cardiovascular center in Puerto Rico or otherwise pay to a private institution for the surgical services provided to the medically indigent patients. Duplication and triplication of such expensive services in a supposedly poor country speaks for a bad utilization of our economic and human resources. In addition, a certain volume of cases are needed to maintain the skills of the cardiovascular surgeons in order to have a low or acceptable mortality.

The functioning of the Cardiovascular Center is not clear, nobody knows exactly how it will function. It has been said that the faculty will be open to all cardiologists in the community, nothing have been said or decided in regard to the cardiovascular surgeons. Since the faculty of the Cardiovascular Center according to the law should be the faculty of the School of Medicine I wholeheartedly recommend a closed faculty, that is, any cardiologist or cardiovascular surgeon must be a member of the University of Puerto Rico School of Medicine. An open faculty will create a two tier system in the same physical plant, introduce problems in education, and produce economic problems, since the outside faculty will not be participating in the School of Medicine Practice Plan as well as problems in quality of care since the outside patients will not be discussed in our departmental meetings, the latter patients will remain in an academic and quality of care limbo. All physicians willing to participate and admit patients to the Cardiovascular Center must obtain an appointment at the School of Medicine, either with a salary or *ad honorem*, then the physician and his patients would follow the same process of admission, treatment, hospital care, discussion of quality of care and economic compensation provided to

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the physicians treating the indigent patient population.

Even accepting that the faculty of the Cardiovascular center will be the faculty of the University of Puerto Rico School of Medicine, the relationship with the Medical, Pediatric, Anesthesiology and Surgical Departments has not been clarified. Again as in the case of the Puerto Rico Medical Center the lines of authority have not been established.

Our future cardiovascular center is supposed to provide services to patients from Central and South America. Although the idea and sense of altruism is excellent I doubt that we will ever get patients from Latin American countries to come to our Island for cardiovascular treatment. Wealthy people from these countries will continue to get their treatment in the large cardiovascular centers of the United States and Puerto Rico is not in such economic position to provide care to the indigent population of neighboring countries. Language does not constitute a barrier since a large number of Hispanics including Puerto Ricans work in those institutions. In addition the multinational American companies are establishing cardiovascular services in Venezuela and Colombia and Argentina already has an excellent center directed by Dr. René Favaloro one of the pioneer surgeons in developing the technique of coronary by-pass surgery. On top of the above, some of our local insurance companies favor and encourage their clients to go to the United States for their specialized cardiovascular treatment. All-inclusive contracts with U.S. hospitals are clearly discriminatory in regard to the professional services they pay in the U.S. versus in Puerto Rico.

The composition of the Board of Directors of the Puerto Rico Cardiovascular Center constitutes a source of conflict. Although the spirit of the law was to create a separate entity, this is contradicted by having the Secretary of Health as president of the Board of Directors. Remember that the Secretary of Health will have to pay for the services provided to the indigent patient, so he or she will be in the awkward position of billing and paying for those services. It is no secret that the Department of Health was, is and will be in deficit and the Secretary of Health will have to set priorities as to how to use his or her limited resources. It could very well be that paying for cardiovascular services might not necessarily be his or her first priority. Remember the Puerto Rico Medical Center was originally created as a public corporation, totally separate and distinct from the Department of Health; later to be placed under the Secretary of Health. Are we following the same route for the Cardiovascular Center? In addition Pediatric Cardiology nor Cardiovascular Surgery are represented in the Board of Directors.

One of the problems confronted by the participating institutions of the Medical Center is the differences in salary created with the initiation of the Puerto Rico Medical Center. This differences has created problems in recruiting nurses and other personnel. The new law creating the Cardiovascular Center by virtue of its exclusive Personnel Office will propitiate the piracy of nurses from other services or institutions within the same governmental structure. It would be specious for us to complain that private Puerto Rican and U.S. hospitals

are recruiting our nurses since we are also doing the same within our own institutions. In fact there is no ethical or moral justification to discriminate as to the services to be provided to a segment of our population while other groups lack some of the more basic needs. I must also mention that there is no waiting list for cardiovascular surgery at the present Cardiovascular Center.

A group of physicians and administrators visited some cardiovascular centers in the United States. They might have obtained some ideas as to the planning and construction of the building but nothing about the administrative functioning of such center. Most of the Cardiovascular Centers in the United States are under the Medical Schools or Health Sciences Centers, others are private hospitals. Our Cardiovascular Center must not be the exception, it must be under the Chancellor and Dean of Medicine of the Medical Sciences Campus.

The Cardiovascular Center for Puerto Rico and the Caribbean is in its infancy. The problems enumerated above must be dealt with and sensible solutions adopted, otherwise administrative and economic chaos will result.

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CARTAS AL EDITOR

El Condón Como Medida de Política Pública Contra el SIDA: Aspectos Éticos y Médicos

El SIDA puede denominarse con justicia el mal del siglo. Son muchas las polémicas que levanta esta controversial enfermedad, que ataca, entre otros, a homosexuales y prostitutas. La que nos ocupa es: ¿Debe el gobierno incluir, dentro de su política pública contra esta enfermedad, una campaña para proveer condones libres de costo a individuos de alto riesgo?

La evidencia médica es la siguiente: los estudios "in vitro" demuestran que el virus HIV-III no atraviesa las membranas de los condones. La evidencia preliminar "in vitro" también señala una disminución en el contagio cuando se usan los métodos de barrera. Sin embargo, como método anticonceptivo sabemos que puede fallar en un 10-15% por rotura, deslizamiento o uso impropio. Este porcentaje pudiera ser mayor en el caso de SIDA, por lo tanto, su uso no ofrece completa seguridad.

A nivel internacional algunos sectores han promovido el uso del condón como agente profiláctico contra el SIDA. En Puerto Rico este asunto ha generado una controversia donde los principales jerarcas del gobierno y de la Iglesia Católica se han pronunciado en contra y la Iglesia Episcopal a favor. Creemos que detrás de este conflicto hay dos visiones éticas encontradas: la ética católica-romana, basada en la ley natural, que considera como inmoral toda relación sexual que no potencialice la concepción (y por tanto rechaza a la homosexualidad y al condón) y la ética protestante, que da énfasis a los méritos de la situación y a sus consecuencias y que no considera la procreación como el único fin legítimo de las relaciones sexuales. Esta visión última no considera moralmente incorrecto que se utilicen métodos de barrera para prevenir el SIDA en aquellos individuos a riesgo que no considerarían la abstinencia.

Una posible solución sería dar prioridad al método de abstinencia en las campañas de prevención de SIDA del gobierno como método más efectivo y presentar al condón de forma real y veraz, como una alternativa, para que sea cada individuo a riesgo quien decida qué modalidad de prevención va a utilizar. Se le releva al gobierno de la distribución de condones y de la responsabilidad de recomendarlos. A la misma vez, se maximiza el bien y se minimiza el mal al proveerle algún tipo de protección contra contagios aún a aquellas personas a riesgo que no abandonarían sus prácticas sexuales.

Carlos A. Acevedo Marrero, MD
Toa Alta, P.R.

¡Una Segunda Oportunidad en la Vida!

A pesar de los continuos esfuerzos de la Asociación Puertorriqueña del Corazón y otras entidades cívicas, aún ocurren en Puerto Rico muchas muertes innecesarias.

Esto ocurre con frecuencia por no iniciar las medidas básicas de resucitación cardiopulmonar con suficiente *rapidez y eficiencia*.

Ocurre tanto en la comunidad, residencias, oficinas, restaurantes, playas, trabajo, etc. como en los mismos hospitales.

No hay duda que hemos progresado pero todavía queda mucho por hacer y debemos persistir hasta lograr nuestro objetivo: ofrecer una segunda oportunidad en la vida a más víctimas de muerte repentina en Puerto Rico.

Es importante lograr ese objetivo mediante un cambio de actitudes y comportamiento de nuestros ciudadanos, legos y profesionales de la salud, en el escenario de una víctima de muerte repentina.

Debemos todos estar preparados para ese día menos pensado que nos encontremos ante una posible víctima de muerte súbita, debemos saber y sentirnos cómodos sobre cómo actuar en tal situación; debemos estar preparados y tener una plan de acción. La dependencia psicológica que sea otro el que se envuelva; de actuar como mero espectador por temor o apatía debe ser vencida por todos, legos o profesionales de la salud.

No se requiere gran capacidad física o mental para aprender bien las técnicas de resucitación. Sin embargo es asombroso ver cómo aún después de recibir un adiestramiento adecuado, muchos persisten en pretender que sean otros los que se envuelven.

Si nos grabamos en nuestras mentes que el cerebro humano sufre daño irreversible si no recibe oxígeno por más de 3 a 5 minutos; si reconocemos que no podemos esperar a que llegue el "experto" que no está presente en esos momentos; si actuamos con prontitud iniciando la respiración y/o circulación artificial (RCP) en ese preciso momento, podremos así ofrecerle a más víctimas de muerte súbita, *¡Una Segunda Oportunidad en la Vida!* Así lograremos reducir la alta tasa de muertes innecesarias en Puerto Rico.

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Rodríguez Torres, Gilberto MD - Escuela de Medicina Universidad Central de Madrid, España, 1963. Oftalmología. Ejerce en Guayama.

Ruiz González, Rafael MD - Escuela de Medicina Universidad Central del Este, República Dominicana, 1980. Medicina Interna. Ejerce en Arroyo.

Santiago Díaz, Santiago MD - Escuela de Medicina Universidad de Zaragoza, España, 1977. Medicina General. Ejerce en Patillas.

Torres Vázquez, Armando MD - Escuela de Medicina Universidad Central del Caribe, Cayey, 1980. Oftalmología. Ejerce en Vega Baja.

Villamil Rodríguez, José R. MD - Escuela de Medicina Universidad de Zaragoza, España, 1976. Medicina Interna. Ejerce en Bayamón.

Vizcarrondo Acosta, Manuel MD - Escuela de Medicina Universidad Central del Este, República Dominicana, 1983. Medicina General. Ejerce en Guayama.

Vizcarrondo Acosta, Nilsa MD - Escuela de Medicina Universidad Central del Este, República Dominicana, 1978. Obstetricia y Ginecología. Ejerce en Guayama.

Zayas Busquets, Egberto MD - Escuela de Medicina Universidad Central del Este, República Dominicana, 1980. Medicina Interna. Ejerce en Guayama.

INTERNOS - RESIDENTES

Izquierdo Encarnación, Natalio MD - Escuela de Medicina de Ponce, 1986. Oftalmología.

Montalvo Bonilla, Luis MD - Escuela de Medicina Universidad Central del Caribe, Cayey, 1985. Oftalmología.

REINGRESOS

Acevedo Maldonado, Jaime MD - Escuela de Medicina Universidad de Sevilla, 1964. Psiquiatría. Ejerce en Río Piedras.

Peraza García, Antonio MD - Escuela de Medicina Universidad de Salamanca, España, 1974. Pediatría. Ejerce en Bayamón.

Sánchez Monserrat, Rafael MD - Escuela de Medicina Universidad de Barcelona, España, 1972. Neumología, Medicina Interna. Ejerce en Río Piedras.

Ricardo Peña, Alberto MD - Escuela de Medicina Universidad de La Habana, Cuba, 1960. Medicina Interna. Ejerce en Hato Rey.

Soto Alarcón, José Luis MD - Escuela de Medicina Universidad de Guadalajara, México, 1977. Medicina General. Ejerce en Hato Rey.

Viana Santos, César MD - Escuela de Medicina San Juan Bautista, 1981. Pediatría. Ejerce en Toa Baja.

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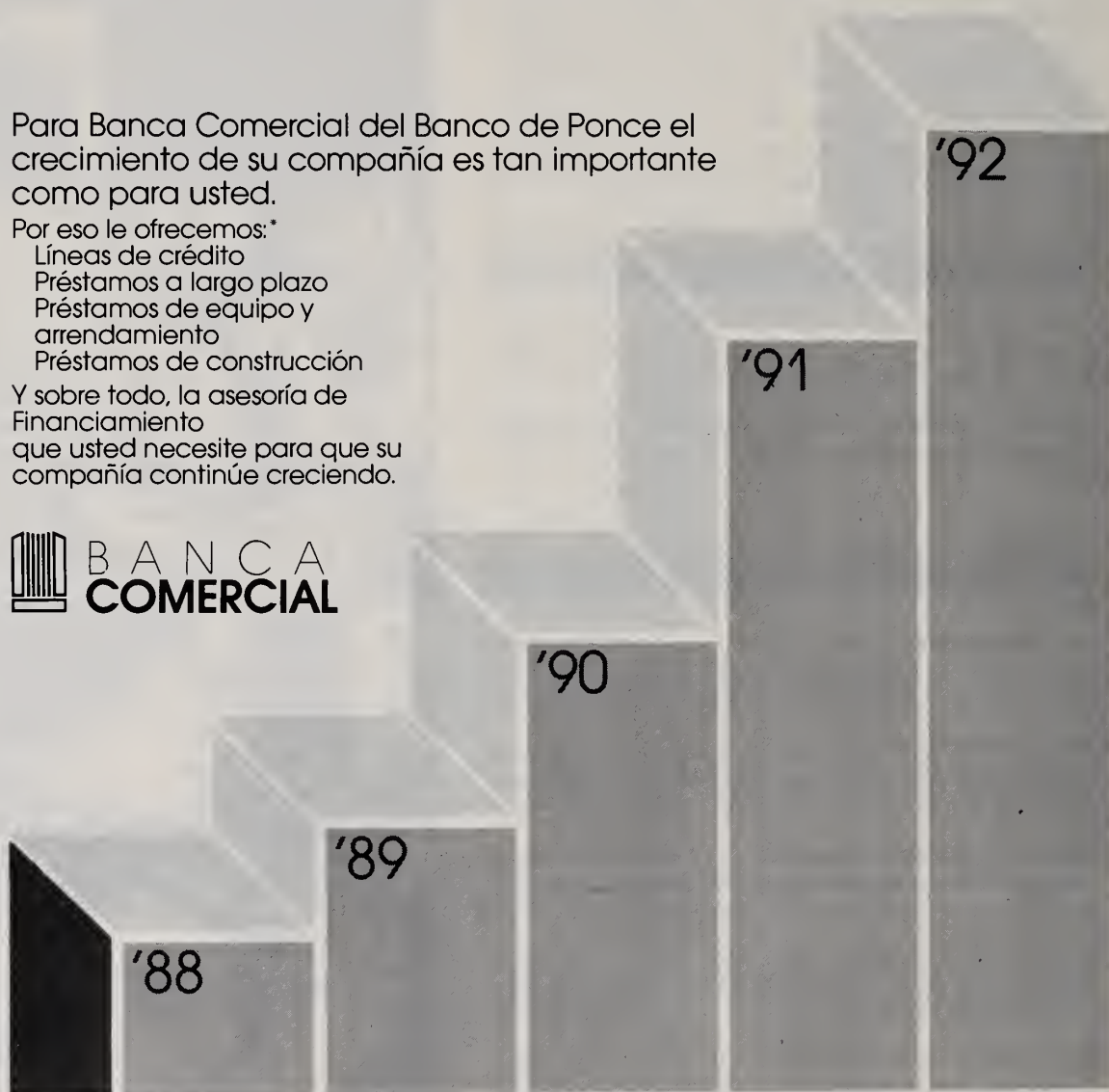
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Uniform Requirements for Manuscripts Submitted to Biomedical Journals

INTERNATIONAL COMMITTEE OF MEDICAL JOURNAL EDITORS*

In January 1978 a group of editors from some major biomedical journals published in English met in Vancouver, British Columbia, and decided on uniform technical requirements for manuscripts to be submitted to their journals. These requirements, including formats for bibliographic references developed for the Vancouver group by the National Library of Medicine, were published in three of the journals early in 1979. The Vancouver group evolved into the International Committee of Medical Journal Editors (ICMJE). At the October 1981 meeting the requirements were revised slightly and published in a second edition in 1982. Since then the group has issued several separate statements, and these have been incorporated into the main part of this, the third, edition.

Over 300 journals have agreed to receive manuscripts prepared in accordance with the initial, previously published, requirements. It is important to emphasize what these requirements imply and what they do not.

Firstly, the requirements are instructions to authors on how to prepare manuscripts, not to editors on publication style. (But many journals have drawn on these requirements for elements of their publication styles).

Secondly, if authors prepare their manuscripts in the style specified in these requirements, editors of the participating journals will not return manuscripts for changes in these details of style. Even so, manuscripts may be altered by journals to conform with details of their own publication styles.

Thirdly, authors sending manuscripts to a participating journals should not try to prepare them in accordance with the publication style of that journal but should

follow the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

Nevertheless, authors "must also follow the instructions to authors in the journal as to what topics are suitable for that journal and the types of papers that may be submitted (for example, original articles, reviews, case reports). In addition, the journal's instructions are likely to contain other requirements unique to that journal, such as number of copies of manuscripts, acceptable languages, length of articles, and approved abbreviations.

Participating journals are expected to state in their instructions to authors that their requirements are in accordance with "Uniform Requirements of Manuscripts Submitted to Biomedical Journals" and to cite a published version.

This document will be revised at intervals. Inquires and comments from Central and North America about these requirements should be sent to Edward J. Huth, M.D., *Annals of Internal Medicine*, 4200 Pine Street, Philadelphia, PA 19104, USA; those from other regions should be sent to Stephen P. Lock, M.D., *British Medical Journal*, British Medical Association, Tavistock Square, London WC1H 9JR, United Kingdom. Note that these two journals provide secretarial services for the International Committee of Medical Journal Editors; they do not handle manuscripts intended for other journals. Papers intended for other journals should be sent directly to the offices of those journals.

Summary of Requirements

Type the manuscript double spaced, including title page, abstract, text, acknowledgments, references, tables, and legends.

Each manuscript component should begin on a new page, in the following sequence.

Title page

Abstract and key words

Text

Acknowledgments

References

Tables: each table, complete with title and footnotes, on a separate page

Legends for illustrations

Illustrations must be good-quality, unmounted glossy prints usually 127 by 173 mm (5 by 7 in.) but no larger than 203 by 254 mm (8 by 10 in.).

Submit the required number of copies of manuscript and figures (see journal's instructions) in a heavy-paper envelope. The submitted manuscript should be accompanied by a covering letter, as described under "Submission of Manuscripts," and permissions to reproduce previously

*Edward J. Huth, M.D.; *Annals of Internal Medicine*, Kathleen King, M.R.C. Path.; *The Medical Journal of Australia* Stephen P. Lock, M.D.; *British Medical Journal*; George D. Lundberg, M.D.; *Journal of the American Medical Association*; Ian Munro, M.B.; *The Lancet*; Magne Nylenna, M.D.; *Tidsskrift for Den Norske Lægeforening*; Roy Rada, M.D.; *Index Medicus*; Arnold S. Relman, M.D.; *New England Journal of Medicine*; Povl Rus, M.D.; *Journal of the Danish Medical Association and Danish Medical Bulletin*; Richard G. Robinson, Ch.M.; *New Zealand Medical Journal*; Bruce P. Squires, M.D.; *Canadian Medical Association Journal*, Dr. Ilkka Vartiomaara; *Finnish Medical Journal*; Malcolm S. M. Watts, M.D.; *The Western Journal of Medicine*.

► Citations of this document should be to one of the sources listed below: INTERNATIONAL COMMITTEE OF MEDICAL JOURNAL EDITORS. Uniform requirements of manuscripts submitted to biomedical journals. *Ann Intern Med*. 1988; 108:258-265 INTERNATIONAL COMMITTEE OF MEDICAL JOURNAL EDITORS. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1988; 296 [In press]

published materials or to use illustrations that may identify human subjects.

Follow the journal's instructions for transfer of copyright. Authors should keep copies of everything submitted.

Prior and Duplicate Publication

Most journals do not wish to consider for publication a paper on work that already has been reported in a published paper or is described in paper submitted or accepted for publication elsewhere. This policy does not usually preclude consideration of a paper that has been rejected by another journal or of a complete report that follows publication of a preliminary report, usually in the form of an abstract. When submitting a paper, an author should always make a full statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same or very similar work. Copies of such material should be included with the submitted paper to help the editor decide how to deal with the matter.

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- (a) The editors of both journals concerned are fully informed; the editor concerned with secondary publication should have a photocopy, reprint, or manuscript of the primary version.
- (b) The priority of the primary publication is respected by a publication interval of at least two weeks.
- (c) The paper for secondary publication is written for a different group of readers and is not simply a translated version of the primary paper; an abbreviated version will often be sufficient.
- (d) The secondary version reflects faithfully the data and interpretations of the primary version.
- (e) A footnote on the title page of the secondary version informs readers, peers, and documenting agencies that the paper was edited, and is being published, for a national audience in parallel with a primary version based on the same data and interpretations. A suitable footnote might read as follows: "This article is based on a study first reported in the [title of journal, with full reference]".

Multiple publication other than as defined above is not acceptable to editors. If authors violate this rule, they may expect appropriate editorial action to be taken.

Preliminary release, usually to public media, of scientific information described in a paper that has been accepted but not yet published is a violation of the policies of many journals. In a few cases, and only by arrangement with the editor, preliminary release of data may be acceptable, for example, to warn the public of health hazards.

Preparation of Manuscript

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279 mm (8½ by 11 in.) or ISO A4 (212 by 297 mm), with margins of at least 25mm (1 in.) Type only on one side of the paper. Use double spacing throughout, including title page, abstract, text, acknowledgment, references, tables, and legends for illustrations. Begin each of the following sections on separate pages; title page, abstract and key words, text, acknowledgment, references, individual tables, and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper or lower right-hand corner of each page.

Title Page

The title page should carry 1) the title of the article, which should be concise but informative; 2) first name, middle initial, and last name of each author, with highest academic degree(s) and institutional affiliation; 3) name of department(s) and institution(s) to which the work should be attributed; 4) disclaimers, if any; 5) name and address of author responsible for correspondence about the manuscript; (6) name and address of author to whom requests for reprints should be addressed, or statement that reprints will not be available from the authors; 7) the source(s) of support in the form of grants, equipment, drugs, or all of these; and 8) a short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified.

Authorship

All persons designated as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content.

Authorship credit should be based only on substantial contributions to (a) conception and design, or analysis and interpretation of data; (b) drafting the article or revising it critically for important intellectual content; and on (c) final approval of the version to be published. Conditions (a), (b), and (c) must all be met. Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is also not sufficient for authorship. Any part of an article critical to its main conclusions must be the responsibility of at least one author.

A paper with corporate (collective) authorship must specify the key persons responsible for the article; others contributing to the work should be recognized separately (see Acknowledgments and Other Information).

Editors may require authors to justify the assignment of authorship.

Abstract and Key Words

The second page should carry an abstract of no more than 150 words. The abstract should state the purposes of the study or investigation; basic procedures (selection of study subjects or experimental animals, observational and analytic methods); main findings (give specific data and their statistical significance, if possible); and the principal conclusions. Emphasize new and important aspects of the study or observations.

Below the abstract, provide, and identify as such, 3 to 10 key words or short phrases that will assist indexers in cross-indexing your article and that may be published with the abstract. Use terms from the Medical Subject Headings (MeSH) list of *Index Medicus*; if suitable MeSH terms are not yet available for recently introduced terms, present terms may be used.

Text

The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Other types of articles such as case reports, reviews, and editorials are likely to need other formats. Authors should consult individual journals for further guidance.

Introduction: State the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively. Do not include data or conclusions from the work being reported.

Methods: Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address within parenthesis marks [round brackets]), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration.

Ethics: When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) or with the Helsinki Declaration of 1975, as revised in 1983. Do not use patients' names, initials, or hospital numbers, especially in any illustrative material. When reporting experiments on animals indicate whether the institution's or the National Research Council's guide for, or any national law on, the care and use of laboratory animals was followed.

Statistics: Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid sole reliance on statistical hypothesis testing, such as the use of *P* values, which fails to convey important quantitative information. Discuss eligibility of experimental subjects. Give details about randomization. Describe the methods for, and success of, any blinding of observations. Report treatment complications. Give numbers of observations. Report losses to observation (such as dropouts from a clinical trial). References for study design and statistical

methods should be to standard works (with pages stated) when possible rather than to papers where designs or methods were originally reported. Specify any general-use computer programs used.

Put general descriptions of methods in the Methods section. When data are summarized in the Results section, specify the statistical methods used to analyze them. Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid non-technical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlation," and "sample." Define statistical terms, abbreviations, and most symbols.

Results: Present your results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables, illustrations, or both; emphasize or summarize only important observations.

Discussion: Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including implications for future research. Relate the observations to other relevant studies. Link the conclusions with the goals of the study but avoid unqualified statement and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

Acknowledgements

At an appropriate place in the article (title-page footnote or appendix to the text; see the journal's requirement) one or more statements should specify: (a) contributions that need acknowledging but do not justify authorship, such as general support by a departmental chairman; (b) acknowledgements of technical help; (c) acknowledgments of financial and material support, specifying the nature of the support; (d) financial relationships that may pose a conflict of interest.

Persons who have contributed intellectually to the paper but whose contributions do not justify authorship may be named and their function or contribution described, for example, "scientific adviser," "critical review of study proposal," "data collection," "participation in clinical trial." Such persons must have given their permission to be named. Authors are responsible for obtaining written permission from persons acknowledged by name because readers may infer their endorsement of the data and conclusions.

Technical help should be acknowledged in a paragraph separate from those acknowledging other contributions.

References

Number references consecutively in the order in which they are first mentioned in the text. Indentify references

in text, tables, and legends by arabic numerals within parenthesis marks. References cited only in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

Use the style of the examples below, which are based on the formats used by the U.S. National Library of Medicine in *Index Medicus*. The titles of journals should be abbreviated according to the style used in *Index Medicus*. Consult *List of Journals Indexed in Index Medicus*, published annually as a separate publication by the Library and as a list in the January issue of *Index Medicus*; also see the list of journal titles and abbreviated titles at the end of this document.

Try to avoid using abstracts as references; "unpublished observations" and "personal communications" may not be used as references, although references to written, not oral, communications may be inserted (within parenthesis marks) in the text. Include among the references papers accepted but not yet published; designate the journal and add "in press" (within parenthesis marks). Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (within parenthesis marks).

The references must be verified by the author(s) against the original documents.

Examples of correct forms of references are given below.

Journals

1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al).
You CH, Lee KY, Chey RY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. *Gastroenterology* 1980; 79:311-4
2. Corporate Author
The Royal Marsden Hospital Bone-Marrow Transplantation Team. Failure of syngeneic bone-marrow graft without preconditioning in post-hepatitis marrow aplasia. *Lancet* 1977; 2:242-4
3. No Author Given
Anonymous. Coffee drinking and cancer of the pancreas [Editorial]. *Br. Med J* 1981; 283:628
4. Journal Supplement
Mastri AR. Neuropathy of diabetic neurogenic bladder. *Ann Intern Med* 1980; 92(2 Pt 2):316-8
Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan [Abstract]. *Blood* 1979; 54(Suppl 1):26a.
5. Journal Paginated by Issue
Seaman WB. The case of the pancreatic pseudocyst. *Hosp Pract* 1981; 16(Sep):24-5

Books and Other Monographs

6. Personal Author(s)
Eisen HN. Immunology: and introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974; 406

7. Editor, Compiler, Chairman as Author
Dausset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973; 12-8
8. Chapter in a Book
Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974; 457-72
9. Published Proceeding Paper
DuPont B. Bone marrow transplantation in severe combined immunodeficiency with an unrelated MLC compatible donor. In: White HJ, Smith R, eds. Proceedings of the third annual meeting of the International Society for Experimental Hematology. Houston: International Society for Experimental Hematology, 1974; 44-6
10. Monograph in a Series
Hunninghake GW, Gadek JE, Szapiel SV, et al. The human alveolar macrophage. In: Harris CC, ed. Cultured human cells and tissues in biomedical research. New York: Academic Press, 1980:54-6. (Stoner GD, ed. Methods and perspectives in cell biology; vol 1).
11. Agency Publication
Ranofsky AL. Surgical operations in short-stay hospitals: United States-1975. Hyattsville, Maryland: National Center for Health Statistics, 1978; DHEW publication no. (PHS)78-1785, (Vital and health statistics; series 13; no 34)
12. Dissertation or Thesis
Cairns RB. Infrared spectroscopic studies of solid oxygen [Dissertation]. Berkeley, California: University of California, 1965. 156 p.

Other Articles

13. Newspaper Article
Shaffer RA. Advances in chemistry are starting to unlock mysteries of the brain: discoveries could help cure alcoholism and insomnia, explain mental illness. How the messengers work. *Wall Street Journal* 1977 Aug 12:1(col 1), 10(col 11).
14. Magazine Article
Roueché B. Annals of medicine: the Santa Claus culture. *The New Yorker* 1971 Sep 4:66-81

Tables

Type each table double spaced on a separated sheet. Do not submit tables as photographs. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all non standard abbreviations that are used in each table. For footnotes, use the following symbols, in this sequence: *, †, ‡, §, II, II, **, ††,....

Identify statistical measures of variations such as standard deviation and standard error of the mean.

Do not use internal horizontal and vertical rules.

Be sure that each table is cited in the text.

If you use data from another published or unpublished

source, obtain permission and acknowledge fully.

The use of too many tables in relation to the length of the text may produce difficulties in the layout of pages. Examine issues of the journal to which you plan to submit your paper to estimate how many tables can be used per 1000 words of text.

The editor, on accepting a paper, may recommend that additional tables containing important back-up data too extensive to publish be deposited with an archival service, such as the National Auxiliary Publication Service (NAPS) in the United States, or made available by the authors. In that event, an appropriate statement will be added to the text. Submit such tables for consideration with the paper.

Illustrations

Submit the required number of complete sets of figures. Figures should be professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Instead of original drawings, roentgenograms, and other material, send sharp, glossy black-and-white photographic prints, usually 127 by 173 mm (5 by 7 in.) but no larger than 203 by 254 mm (8 by 10 in.). Letters, numbers, and symbols should be clear and even throughout, and of sufficient size that when reduced for publication each item will still be legible. Titles and detailed explanations belong in the legends for illustrations, not on the illustrations themselves.

Each figure should have a label pasted on its back indicating the number of the figure, author name, and the top of the figure. Do not write on the back of the figures, or scratch or mar them using paper clips. Do not bend figures or mount them on cardboard.

Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with the background.

If photographs of persons are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.

Figures should be numbered consecutively according to the order in which they have been first cited in the text. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required, irrespective of authorship or publisher, except for documents in the public domain.

For illustrations in color, ascertain whether the journal requires color negatives, positive transparencies, or color prints. Accompanying drawings marked to indicate the region to be reproduced may be useful to the editor. Some journals publish illustrations in color only if the author pays for the extra cost.

Legends for Illustrations

Type legends for illustrations double spaced, starting on a separate page, with arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

Explain internal scale and identify method of staining in photomicrographs.

Units of Measurement

Measurements of length, weight, and volume should be reported in metric units (metre, kilogram, litre) or their decimal multiples.

Temperatures should be given in degrees Celsius. Blood pressures should be given in millimetres of mercury.

All hematologic and clinical chemistry measurements should be reported in the metric system in terms of the International System of Units (SI). Editors may request that alternative or non-SI units be added by the author before publication.

Abbreviations and Symbols

Use only standard abbreviations. Avoid abbreviations in the title and abstract. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

Submission of Manuscripts

Mail the required number of manuscript copies in a heavy-paper envelope, enclosing the manuscript copies and figures in cardboard, if necessary, to prevent bending of photographs during mail handling. Place photographs and transparencies in a separate heavy-paper envelope.

Manuscripts must be accompanied by a covering letter. This must include (a) information on prior or duplicate publication or submission elsewhere of any part of the work; (b) a statement of financial or other relationships that might lead to a conflict of interest; (c) a statement that the manuscript has been read and approved by all authors; and (d) the name, address, and telephone number of the corresponding author, who is responsible for communicating with the other authors about revisions and final approval of the proofs. The letter should give any additional information that may be helpful to the editor, such as the type of article in the particular journal the manuscript represents and whether the author(s) will be willing to meet the cost of reproducing color illustrations.

The manuscript must be accompanied by copies of any permissions to reproduce published material, to use illustrations or report sensitive personal information of identifiable persons, or to name persons for their contributions.

Participating Journals

The journals listed in Table I are those that notified the ICMJE of their willingness to consider for publication manuscripts prepared in accordance with the guidance given in the second (1982) edition of the Uniform Requirements for the Submission of Manuscripts to Biomedical Journals. Their listing here does not imply that they endorse this present version (3rd) of "Uniform Requirements...". The *Index Medicus* abbreviations for journal titles are given within square brackets.

Table 1 Journals Participating in the Uniform Requirements Agreement

<i>Acta Medica Colombiana</i> [Acta Med Colomb]	<i>British Heart Journal</i> [Br Heart J]
<i>Acta Orthopaedica Scandinavica</i> [Acta Orthop Scand]	<i>British Homoeopathic Journal</i> [Br Homoeopath J]
<i>Acta Paediatrica Japonica</i> [Acta Paediatr Jpn (Overseas)]	<i>British Journal of Anaesthesia</i> [Br J Anaesth]
<i>Acta Paediatrica Scandinavica</i> [Acta Paediatr Scand]	<i>British Journal of Industrial Medicine</i> [Br J Ind Med]
<i>Acta Pharmacologica Sinica</i> [Acta Pharmacol Sin]	<i>British Journal of Occupational Therapy</i> [Br J Occup Ther]
<i>Activox</i> [Activox]	<i>British Journal of Ophthalmology</i> [Br J Ophthalmol]
<i>AIDS: An International Bimonthly Journal</i> [AIDS]	<i>British Journal of Pain</i> [Br J Pain]
<i>American Family Physician</i> [Am Fam Physician]	<i>British Journal of Rheumatology</i> [Br J Rheumatol]
<i>The American Journal of Cardiology</i> [Am J Cardiol]	<i>British Journal of Surgery</i> [Br J Surg]
<i>The American Journal of Clinical Nutrition</i> [Am J Clin Nutr]	<i>British Medical Bulletin</i> [Br Med Bull]
<i>American Journal of Diseases of Children</i> [Am J Dis Child]	<i>British Medical Journal</i> [Br Med J]
<i>The American Journal of Emergency Medicine</i> [Am J Emerg Med]	<i>Bulletin of the Medical Library Association</i> [Bull Med Libr Assoc]
<i>American Journal of Epidemiology</i> [Am J Epidemiol]	<i>British Osteopathic Journal</i> [Br Osteopath J]
<i>American Journal of Hospital Pharmacy</i> [Am J Hosp Pharm]	<i>Bulletin of the World Health Organization</i> [Bull WHO]
<i>The American Journal of Human Genetics</i> [Am J Hum Genet]	<i>Canadian Family Physician</i> [Can Fam Physician]
<i>The American Journal of Medicine</i> [Am J Med]	<i>Canadian Journal of Anaesthesia</i> [Can J Anaesth]
<i>American Journal of Obstetrics and Gynecology</i> [Am J Obstet Gynecol]	<i>Canadian Journal of Comparative Medicine</i> [Can J Comp Med]
<i>American Journal of Optometry and Physiological Optics</i> [Am J Optom Physiol Opt]	<i>Canadian Journal of Public Health</i> [Can J Public Health]
<i>The American Journal of Pathology</i> [Am J Pathol]	<i>Canadian Journal of Surgery</i> [Can J Surg]
<i>The American Journal of Psychiatry</i> [Am J Psychiatry]	<i>Canadian Medical Association Journal</i> [Can Med Assoc J]
<i>The American Journal of Public Health</i> [Am J Public Health]	<i>Canadian Veterinary Journal</i> [Can Vet J]
<i>AJR: American Journal of Roentgenology</i> [Am J Roentgenol]	<i>Cardiovascular Research</i> [Cardiovasc Res]
<i>The American Journal of Surgery</i> [Am J Surg]	<i>Central African Journal of Medicine</i> [Cent Afr J Med]
<i>American Review of Respiratory Disease</i> [Am Rev Respir Dis]	<i>Cephalgia</i> [Cephalalgia]
<i>The American Surgeon</i> [Am Surg]	<i>Chest</i> [Chest]
<i>Anaesthesia</i> [Anaesthesia]	<i>Chinese Journal of Anesthesiology</i> [Chin J Anesthesiol]
<i>Anaesthesia and Intensive Care</i> [Anaesth Intensive Care]	<i>Chinese Journal of Cardiovascular Disease</i> [Chin J Cardiovasc Dis]
<i>Anesthesia and Analgesia</i> [Anesth Analg]	<i>Chinese Journal of Dermatology</i> [Chin J Dermatol]
<i>Annals of Clinical Biochemistry</i> [Ann Clin Biochem]	<i>Chinese Journal of Digestion</i> [Chin J Dig]
<i>Annals of Clinical and Laboratory Science</i> [Ann Clin Lab Sci]	<i>Chinese Journal of Endocrinology and Metabolism</i> [Chin J Endocrinol Metab]
<i>Annals of Internal Medicine</i> [Ann Intern Med]	<i>Chinese Journal of Epidemiology</i> [Chin J Epidemiol]
<i>The Annals of Otolaryngology, Rhinology and Laryngology</i> [Ann Otol Rhinol Laryngol]	<i>Chinese Journal of Experimental Surgery</i> [Chin J Exp Surg]
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AAP RECOMMENDS CHOLESTEROL SCREENING FOR YOUNG CHILDREN AT RISK

The American Academy of Pediatrics (AAP) today recommended that children over the age of two with a family history of elevated blood-fat levels (hyperlipidemia) or early coronary heart disease should receive regular cholesterol testing. The AAP, however, does not recommend universal cholesterol testing of all children.

In a policy statement published in the October issue of *AAP News*, and released at the Academy's Annual Meeting in San Francisco, the AAP's Committee on Nutrition suggests regular elective testing of children more than two years of age with a family history (parent, sibling, grandparent, uncle or aunt) of hyperlipidemia or early myocardial infarction (before age 50 in men, 60 in women).

"The values that may predict future coronary heart disease are not yet established in children, but children with values persistently exceeding the 75th percentile (176 mg/dL) for plasma cholesterol should be considered for dietary counseling, which is the level recommended for adult dietary intervention," according to the Committee.

For children with borderline and elevated values, several tests in the fasting state should be obtained including total cholesterol, triglyceride and high-density lipoprotein (HDL) cholesterol levels.

The Committee does not favor universal testing of cholesterol levels of children for the following reasons:

1. The standardization of equipment and the measurement of cholesterol are fraught with difficulties.
2. Many of the instruments suggested for the measurement of cholesterol in the office have not been adequately standardized for *field* conditions. Moreover, proper performance of this laboratory procedure requires technical skill not always available in the office.

3. A single blood cholesterol level in children may not reflect daily, day-to-day, and seasonal variations. Thus, measurements obtained over several months may be required to identify those children with persistent elevations.
4. A sporadic elevated concentration of cholesterol in a child with no high-risk family history of coronary heart disease could lead to the initiation of severe dietary (or even drug) control that would be extremely difficult to maintain in a growing child. In fact, such an unwarranted diet or treatment could have a harmful effect to growth and development.

AAP DISCOURAGES INFANT EXERCISE PROGRAMS

The American Academy of Pediatrics (AAP) has recommended against structured exercise programs for infants, arguing that no data exist to suggest these programs will advance skills or provide any long-term benefits to normal infants.

In a policy statement published in the October issue of *AAP News*, the AAP's Committee on Sports Medicine said that infant exercise programs are becoming abundant in the United States. Most programs involve massage techniques and passive exercises. Some involve the purchase of exercise equipment.

"Promoters have claimed that participation by an infant in these programs will improve physical prowess," the Academy's Committee said. But, the "possibility exists that adults may inadvertently exceed the infant's physical limitations by using structured exercise programs."

The statement noted that infant exercise programs should not be promoted as being therapeutically beneficial for the development of healthy infants.

However, providing a stimulating environment for an infant's development is extremely important, the Committee said. They continued that parents do not need specialized skills or equipment to provide an environment for the optimum development of their infant.

"An infant should be provided with opportunities for touching, holding, face-to-face contact, and minimally structured playing with safe toys. If these opportunities occur, infant's intrinsic motivation will guide his or her individual development course," the Committee concluded.

EAR TUBE CONTROVERSY CONTINUES

A controversy that has been raging for over 30 years still has pediatricians debating the remedy for chronic otitis media with effusion, a common childhood ear

disease— whether or not to use ear tubes.

"Although we have, in the past ten years, conducted clinical trials and narrowed down the indications for ear tubes, the medical community still cannot make a blanket statement about who should and should not have tubes," said Charles Bluestone, M.D., an Otolaryngologist at the Children's Hospital of Pittsburgh.

Otitis media is an inflammation of the middle ear cavity. In young children, the fluid build-up usually disappears in about three months—sometimes sooner.

Originally advocated in the 19th century, ear tubes were reintroduced to remedy the fluid accumulation, but didn't become popular until the 1960s. At that time, however, there were no studies to prove their efficacy and safety. For this reason, many doctors opposed the insertion of ear tubes. Although hard data now exists indicating the benefits of their use in certain situations, some doctors still oppose them.

"When ear tubes first caught on I wrote warnings against them," said Gunnar Stickler, M.D., an opponent of ear tubes and a pediatrician at the Mayo Clinic in Rochester, Minnesota. "And now that studies have been done, I'm still not convinced that inserting the tubes is better than using antibiotics and waiting until the fluid disappears."

Dr. Stickler also opposes the use of ear tubes because he feels they can be recommended too often without clear knowledge of their long-term effects on speech, language and intellectual development. Dr. Stickler has, in fact, called for a moratorium on the use of ear tubes.

Studies have indicated that two groups of children are strong candidates for ear tubes: those who experience chronic middle ear effusion (fluid) for three months or longer and who are unresponsive to antibiotics; and children who have frequently recurrent acute middle ear infections that are also unresponsive to antibiotic treatment.

Dr. Bluestone commented, though, that for these two groups of children there are still other variables that have to be considered before tubes are recommended.

"The indications for ear tubes are very conservative," Dr. Bluestone said. "Every child should be evaluated individually."

of alcohol abuse, the new warning labels are a significant step."

By December 1989, all containers of beer, wine and liquor will for the first time be required to bear a warning label reading:

"GOVERNMENT WARNING: 1) According to the Surgeon General, women should not drink alcoholic beverages during pregnancy because of the risk of birth defects. 2) Consumption of alcoholic beverages impairs your ability to drive a car or operate machinery, and may cause other health problems."

Although similar warning label legislation has been considered by Congress for more than a decade, this new requirement was included in the omnibus drug bill passed October 21. President Reagan is expected to sign the bill into law.

Five thousand babies born in the United States each year suffer from FAS, which can occur when pregnant women drink excessively. As many as 50,000 newborns suffer a milder form of alcohol-related birth defects known as fetal alcohol effects. FAS is characterized by a cluster of abnormalities including: prenatal and post-natal growth deficiency; facial malformations, including a small head circumference, flattened midface, sunken nasal bridge and a flattened and elongated philtrum (the groove between the nose and the upper lip); central nervous system dysfunction; and varying degrees of major organ system malformations.

According to Kenneth L. Jones, M.D., director of the California Teratogen Registry, which focuses its attention on agents harmful to unborn children, recent studies link an average of one to two drinks daily to decreased birth weight, growth abnormalities and behavioral problems in the newborn and infant. Increased risk of spontaneous abortion has been found at an even lower consumption of one to two drinks, twice weekly.

"There is no established safe dose of alcohol during pregnancy, nor does there appear to be a safe time to drink," Dr. Jones said. "What is clear is that whenever drinking is stopped during pregnancy, the risk of alcohol effects and consequences of alcohol exposure are decreased."

NEW ALCOHOL WARNING LAW WILL RAISE AWARENESS OF FETAL ALCOHOL SYNDROME

A new federal law requiring warning labels on all alcoholic beverages will make millions more men and women aware that consumption of alcohol can cause serious birth defects, according to the American Academy of Pediatrics (AAP).

"Too many people do not know that Fetal Alcohol Syndrome (FAS) exists, much less that it is the third leading cause of birth defects in this country, and of these, the only preventable one," said Donald W. Schiff, M.D., AAP president. "Although we must continue more comprehensive education efforts about the many dangers

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HIV BABIES RUN STEEP HOSPITAL BILLS; SOME INPATIENT CARE UNNEEDED

Children infected with the AIDS-causing human immunodeficiency virus (HIV) are running up steep hospital bills, their care made especially expensive by the severity of their illness and social costs associated with their cases, a study in JAMA says.

The report, by James D. Hegarty, MPH, and colleagues at the Harlem Hospital Center, New York City, finds hospital care for 37 HIV-infected children treated at that institution from 1981 through 1986 cost a total of nearly \$3.4 million. Lifetime care averaged \$90,347 per child, with one-third of total inpatient days and 20 percent of costs resulting from social rather than medical factors.

"The unique needs of human immunodeficiency virus-infected children require innovative medical, social, and financial solutions," the report says.

But a related study suggests a significant proportion of the inpatient care for HIV-positive children appears to be medically unnecessary, and the cost of this care could be reduced substantially by improved medical and social services.

This second study, by Kathi Kemper, MD, MPH, now of the University of Washington and Harborview Medical Center, Seattle, and Brian Forsyth, MD, ChB, of the Yale University School of Medicine, New Haven, Conn., analyzed hospital use by 34 HIV-positive children seen at Yale-New Haven Hospital from 1983 through October 1987. Overall, 54 percent of the children's inpatient stays were judged medically unnecessary, based on a standardized appropriateness evaluation protocol.

This rate of unnecessary hospitalization declined from 64 percent of all hospital days in 1983 and 1984 to 30 percent in 1987 "as a result of improved outpatient services and access to foster care," the authors report. Still, they note, the rate is higher than the 18 to 25 percent in general pediatric patients in New England and the 20 percent reported at a large Midwestern university hospital.

"The large differences in results between this and earlier studies are almost certainly due to the difficult social situations these children are in and the stigma of

being HIV-positive," the authors say. These children often were hospitalized longer because their "frequently chaotic home lives" made it difficult to discharge them to their parents, or because they suffered the effect of being "labeled," their seropositivity often taken for "a diagnosis of HIV infection or AIDS or as indicating the need for strict isolation." In 10 cases, the report notes, children initially labeled HIV-positive eventually became seronegative, likely a result of their losing maternal HIV antibodies.

Unneeded hospitalizations fell as hospital and social service officials gained experience with such children. "Whether stimulated by concerns over exponentially rising health care costs or compassion for these unfortunate children, improved access to outpatient medical services and stronger family services and foster care programs are the keys to reducing the proportion of medically unnecessary pediatric inpatient stays among HIV + children," the authors write.

The New York study found the daily cost of hospital care for HIV-infected children was highest for those with opportunistic infections (\$705) and lowest (\$466) for homeless "boarder babies," those who remained in the hospital because they had nowhere else to go. Boarder babies had an average length of stay nearly four times that of children who had homes (339 days versus 89 days). Children whose mothers were intravenous drug users also stayed in the hospital longer.

But even after adjusting for "social days," the children averaged 101 inpatient hospital days annually—63 percent more than the average annual hospitalizations for adult AIDS patients in Massachusetts, the authors say. "Thus, even if the boarder baby dilemma were immediately solved, the severity of pediatric HIV disease, which results in multiple and prolonged hospitalizations, would continue to make care for infected children extremely expensive," they say.

"The cumulative cost of care represents far more than the expenses of medical need," the study concludes. "Humane and civilized living conditions... should be ensured for these children. Our nation must develop coherent, comprehensive programs that include improved housing, home care, and respite care for this group of disadvantaged and chronically ill children."

JAMA October 7, 1988

REPORT: AIDS RATE AMONG HETEROSEXUALS KEEPING PACE WITH OTHER GROUPS

AIDS is not sweeping through the U.S. heterosexual population, but reported cases of AIDS spread through heterosexual contact have kept pace with infection rates among other risk groups, says a report in JAMA. Intravenous drug use is cited as a key factor.

"Although AIDS is not 'exploding' into the heterosexual population relative to other risk groups," write authors Harry W. Hawerkos, MD, of the National Institute on Drug Abuse, Rockville, MD, and Robert Edelman, MD, of the National Institute of Allergy and Infectious Diseases, Bethesda, MD, "the increase in the number of heterosexual cases is proportional to increases in other risk groups."

Fifty-two percent of all heterosexual AIDS cases reported since 1981 were diagnosed and reported between Jan. 1, 1987, and April 1988, the authors say. "Similarly, 51 percent of all AIDS cases reported in the United States since 1981 have been reported during the same period, suggesting that the proportion of heterosexual cases has not increased relative to other risk groups."

Research points to intravenous drug abuse as "an important link" in the heterosexual and pediatric spread of the AIDS-causing human immunodeficiency virus (HIV), the authors say. Sixty-one percent of U.S.-born heterosexual AIDS patients reported sexual contact with an IV drug abuser, and 56 percent of mothers with infected children were IV drug abusers. Another 18 percent of such women were sexual partners of IV drug abusers.

Heterosexual spread of AIDS also appears to be more of a problem among blacks than whites in the U.S., the authors note. Blacks account for 26 percent of all AIDS cases in the United States, but for 51 percent of heterosexual IV drug abusers with AIDS, 69 percent of AIDS cases attributed to heterosexual contact, and 61 percent of pediatric AIDS patients whose parents are at risk for AIDS. There also are more Hispanics than whites among IV drug users and children with AIDS.

In an accompanying editorial, H. Hunter Handsfield, MD, of the University of Washington School of Medicine, Seattle, says "there is no question that the problem will grow, but it seems likely that the rate of heterosexual transmission of HIV in North America is limited in part by relatively inefficient female to male spread." However, he notes, "this situation could change".

"For example, if the efficiency of HIV transmission increases with time and deteriorating immune function, the growing pool of women infected by needle sharing or by sexual exposure may become progressively more efficient transmitters of the virus. In the meantime, health officials and funding agencies must assume and prepare for the worst," he says.

"The allocation of resources for the needed behavioral changes will pay great dividends in the prevention of all (sexually transmitted diseases) and their sequelae, including AIDS, and widespread, aggressive measures to modify sexual and drug abuse behaviors remain among the highest international health priorities."

According to Hawerkos and Edelman, condoms still offer the best protection outside of abstinence to prevent HIV spread. One study involving spouses of AIDS patients showed that those who used condoms were less likely to be infected (1 in 10) than those who did not use condoms (12 of 14), they say.

"It is not clear how far or how fast HIV infection will

spread into the heterosexual population of the United States... however, there can be no doubt that heterosexual transmission occurs," the report concludes. "From our perspective, AIDS is preponderantly a sexually transmitted disease and can be transmitted from man to man, man to woman, and woman to man." There are even suggestions of possible woman to woman transmission, the authors note.

The report cautions that because of AIDS' "apparent foothold in the heterosexual community, societies may soon have to wrestle with many difficult questions, including notification of sexual partners and the suitability of infected individuals for marriage and natural parenthood."

JAMA October 7, 1988

PREMARITAL HIV TESTING

Mandatory premarital human immunodeficiency virus (HIV) testing has been criticized as expensive and inefficient, and a letter in JAMA supports this view—at least in one state with such a testing policy. The Illinois testing program spotted only five HIV-positive persons during the first four months of 1988, out of nearly 45,000 marriage license applicants, write Edward A. Belongia, MD, of the Wisconsin Division of Health, Madison, and colleagues. Each of the five had identified HIV risk factors, although it's unclear whether the prospective spouses knew that. Based on estimated testing and physician charges, the authors figure it cost more than \$715,000 for each HIV case confirmed. "Despite this high cost, there is no evidence that HIV infections have been prevented as a result of the program," they say. They also note that many couples get around the Illinois law by going to neighboring Wisconsin to obtain marriage licenses. The number of Illinois couples married in Wisconsin in the first quarter of 1988 quadrupled from a year earlier, with most of the marriages occurring in border counties.

JAMA October 7, 1988

SUDDEN INFANT DEATH DESPITE USE OF HOME MONITORS

A home cardiorespiratory monitor is often recommended for infants considered at high risk for Sudden Infant Death Syndrome (SIDS). But parents don't always use the devices properly, and follow-up of such children needs to be significantly improved, says a study in October's *American Journal of Disease of Children, AJDC*. The report, by Robert G. Meny, MD, of the University of Maryland School of Medicine, Baltimore, and colleagues, describes 10 infants who died suddenly and unexpectedly over a two-year period—nine of SIDS—despite the availability of a home monitor.

"Noncompliance with proper monitoring technique occurred in a majority of the study patients; methods of educating parents of infants at high risk of sudden infant death syndrome with the necessity for compliance need to be developed," the study says. Most of the infants studied came from poor homes—typical of infants at increased SIDS risk. In an accompanying editorial, Robert C. Beckerman, MD, of the Tulane University School of Medicine, New Orleans, agrees that infants at risk for SIDS "should not only be monitored at home but also be intensively followed up by a home care program."

SKIN FLOURESCENCE AS POTENTIAL SUN DAMAGE MEASURE

A report in October's *Archives of Dermatology* describes a technique that may allow non-invasive evaluation of sun-caused skin damage by means of fluorescence—studying the light patterns certain skin components emit when exposed to laser light. Two major compounds of skin, elastin and collagen, are known to emit fluorescence patterns when exposed to light of certain wavelengths, notes the report by David J. Leffell, MD, of the Yale University School of Medicine, New Haven, Conn., and colleagues. The authors used this technique to determine whether they could detect skin damage—alterations in elastin and collagen—caused by sun exposure. They studied skin fluorescence patterns in 28 people, shining ultraviolet light from a laser on various sun-exposed and unexposed skin sites. They say the exposed and non-exposed areas emitted different fluorescence spectra that appeared unrelated to age, pigmentation, or skin thickness—suggesting the differences were due to solar radiation. Although all of the implications of these findings are as yet unclear, "the observation of *in vivo* tissue fluorescence may be utilized to develop a marker of photoaging."

DECIDING WHEN NOT TO RESUSCITATE

Cardiopulmonary resuscitation (CPR) should be administered only to patients who may benefit from this costly and emotionally and physically traumatic procedure, a study in *JAMA* says.

Since its introduction 25 years ago, CPR has become standard procedure in hospitals, although a majority of patients undergo the procedure with little or no clear benefit, says George E. Taffet, MD, and colleagues at the Veterans Administration Medical Center, Houston.

Contrary to some reports in the medical literature that suggest patient age is not a determinant in the outcome of CPR, the authors found that an age of 70 or more in their study population was associated with poor outcome after in-hospital resuscitation. In their retrospective study of 77 resuscitation efforts involving patients aged 70 or older, only 22 (29 percent) were alive after 24 hours, and none lived to discharge. In 322 CPR efforts involving

younger patients, however, 137 were alive after 24 hours and 22 (16 percent) survived to discharge.

They also found that the presence of infections or cancer predicted poor outcome, as did the fact that cardiac arrest occurred unobserved. Of 89 patients with cancer undergoing CPR, only 37 percent were successfully resuscitated and none lived to discharge, while 21 (8.8 percent) of 240 patients without cancer who underwent CPR lived to discharge. Only one of 73 patients with infections receiving CPR survived to discharge, compared with 20 (7.8 percent) of 256 patients without infection.

The authors say their findings should help physicians discuss with patients and their families, at the time of admission to the hospital, whether or not to choose resuscitation. Also, they write, when responding to an arrest, "the age of the patient and knowledge of whether the arrest was observed may give the physician some insight into whether the patient is likely to survive to discharge. After the resuscitation effort is in progress, the number of medication doses as well as the duration of CPR may give a sense of when to stop the effort."

These findings apply to sick, aged, male Veterans Administration hospital patients and may not be applicable to other populations, other settings, or any given patient, the authors caution. While CPR should not be withheld from all patients older than 70 years, "selection of candidates for this emotionally and physically injurious procedure must be made carefully. Cardiopulmonary resuscitation is a traumatic, time-consuming, and expensive technology that should be reserved for those for whom there is a reasonable chance of survival to discharge."

In a related commentary, David L. Schiedermayer, MD, of the Medical College of Wisconsin, Milwaukee, warns against using age alone as a criteria for do-not-resuscitate (DNR) orders. "The study by Taffet et al can be used in conjunction with other data to enable physicians to make more informed recommendations to patients and families about resuscitation," he writes. He also cautions that "cardiopulmonary resuscitation should not be withheld from individual patients based solely on the physician's unilateral assessment of futility."

In a related report, Donald J. Murphy, MD, of the Harvard Medical School, Boston, proposes a change in current policies regarding DNR orders involving the very old, severely demented or chronically ill patients in long-term care institutions. Murphy recommends that physicians be allowed to make unilateral decisions regarding the withholding of CPR from such cases, because, he writes, the procedure "is rarely effective, and in many cases futile in this population"; most informed patients in long-term care institutions do not want resuscitation; "physicians are not required to provide or discuss useless therapy with patients"; and "recent court cases support the withholding of useless therapy."

Murphy describes his clinical experiences, which, like those of others, suggest few informed elderly patients want CPR. He reports that after providing patients with detailed information about their conditions, what CPR involves, and what the intensive care unit experience is

like, 23 of 24 opposed resuscitation.

Although unilateral decisions by health care teams may be criticized as paternalistic, paternalism may be justified in some situations, Murphy writes. "Although the overwhelming consensus is that we must discuss resuscitation with all patients before a DNR order can be written, this mandate may not be appropriate for long-term care institutions where such therapy is often futile or can be harmful if it prevents a timely death... Without a modicum of potential benefit, the patient (or guardian if the patient is demented) has no right to expect this useless therapy. Administration of such therapy would be irresponsible. Therefore, care givers should have no obligation to discuss this useless therapy."

An accompanying commentary by Stuart J. Youngner MD, of the Case Western Reserve University School of Medicine, Cleveland, disagrees with Murphy's proposal. "Living for five more days might give some patients the opportunity to say goodbyes, to wait for the arrival of a loved one from another city, or to live to see the birth of a grandchild," he writes. The disability and pain that is intolerable for one person may not be so for another, he says.

"Murphy's proposal is a regressive step. Under the guise of medical expertise and concern for proper resource allocation, it encourages physicians to substitute their own value judgments for those of their patients," Youngner writes. Unlike his proposal, Murphy's clinical actions were eminently reasonable and extremely effective: He provided patients and their families with "accurate descriptions of their medical conditions and prognoses, and the grisly realities of dying in a critical care unit," Youngner says. But after giving ample evidence to the contrary, Murphy still believes families may not always choose what is in the patient's best interest.

Murphy's actions are much more appealing than his proposal, Youngner concludes. "By engaging in honest communication, he was able to use his clinical knowledge and judgment to help families and patients make wise choices about painful but inescapable issues. Physicians would do well to follow Dr. Murphy's example—not his proposal."

JAMA October 14, 1988

GENETIC EVIDENCE, POSSIBLE BIOLOGIC MARKER IN ALZHEIMER'S DISEASE

There is increasing evidence that Alzheimer's disease has a strong genetic component. A study in October's *Archives of General Psychiatry* supports this view and also suggests a possible biologic marker for one prominent subgroup of Alzheimer's patients, those whose symptoms develop early and progress rapidly. Authors George S. Zubenko, MD, PhD, of the Western Psychiatric Institute and Clinic, Pittsburgh, and colleagues studied first-degree relatives (father, mother, sister, brother, etc.) of 43 probable Alzheimer's patients and 47 healthy controls. Relatives of patients had about a

50 percent lifetime risk of dementia, more than four times that of the controls. The authors then looked at the study subjects' platelet membrane fluidity, and index of membrane rigidity. Relatives of patients with increased platelet membrane fluidity who developed dementia showed symptoms much earlier than relatives of patients without this abnormality. A second *Archives* study, by Ronald L. Martin, MD, of the University of Kansas School of Medicine, Wichita, and colleagues, also offers evidence of a genetic link in Alzheimer's. This study, of 22 Alzheimer's patients and 24 controls, found that relatives of patients had a 41 percent risk of developing Alzheimer's by age 83—double that of the controls. The authors note that study subjects "were not selected on the basis of factors posited by some to indicate a familial form of (Alzheimer's), suggesting that such a genetic mechanism may be involved in the occurrence of (Alzheimer's) in general."

DRUG MAY EASE FATIGUE IN MULTIPLE SCLEROSIS

Amantadine, an antiviral drug used to treat some patients with parkinsonism, also may help to ease one of the major complaints in multiple sclerosis—fatigue, says a study in October's *Archives of Neurology*. The report, by Gary A. Rosenberg, MD, and Otto Appenzeller, MD, PhD, of the University of New Mexico School of Medicine, Albuquerque, describes a double-blind, placebo-controlled study of amantadine's effects in 10 multiple sclerosis patients. Six of the 10 reported that the drug greatly helped their fatigability. The authors also note that amantadine therapy was accompanied by measurable changes in the patients' levels of the naturally occurring opioid chemicals beta-endorphin-beta lipotropin. "We have not presented evidence that amantadine is useful in the treatment of multiple sclerosis," they caution, "but suggest only that it is helpful in the management of the central component of fatigue in some patients."

TPA APPROVAL CONTROVERSY EXPLAINED BY ADVISORY COMMITTEE

Last year's delay in Food and Drug Administration approval for the blood clot-busting drug TPA, or tissue plasminogen activator, reflected appropriate advice by the FDA's Cardiovascular and Renal Drugs Advisory Panel, panel members write in *JAMA*.

Peter R. Kowey, MD, of the Medical College of Pennsylvania, Philadelphia, and other members of the advisory panel criticize news media pressure to quickly approve TPA and applaud the FDA's "careful reconsideration" in approving the drug for general use, which came six months after the original advisory panel recommendation to postpone approval.

Intravenous recombinant TPA is an enzyme used to

break down blood clots, particularly in the vessels of the heart muscle following heart attack. As with other clot-dissolving drugs, there is a risk of internal bleeding associated with its use. The FDA, at the suggestion of its advisory panel, postponed approval "pending further data analysis and to ask the sponsor to provide FDA with the results of ongoing trials when they were available."

Newspaper editorials called for FDA Commissioner Frank Young to dismiss the panel's advice and grant immediate approval to TPA. Despite public pressure, the FDA refused, but did agree to expedite the review process when the sponsor, Genentech, Inc., of South San Francisco, Calif., provided additional information to support its application.

"The FDA, to its credit, did not succumb to the media campaign. Commissioner Young and his staff endorsed the committee's findings but, most appropriately, did promise to expedite review of any new information the sponsor wished to present in support of the application," say the authors.

Prior to the approval hearing, *The Wall Street Journal* published an editorial calling for immediate release of TPA. The panel members label the arguments made in the editorial as theoretical and say evidence at the hearing "led the committee to believe that the drug was not approvable as presented."

The advisory panel says its findings were publicly challenged by the news media, notably *The Wall Street Journal*, which argued that the postponement decision would "sacrifice thousands of American lives on an altar of pedantry." Panel members say they were surprised that the "most vociferous critics were members of the lay press, who had expertise not in medicine but in financial matters."

Some physicians joined the news media in criticizing the panel for lack of economic or medical foresight in its decision. But the advisory panel defends its action by arguing that "intuition cannot substitute for scientific method." In the end, the authors write, "no final determination regarding safety could be made," and, based on the data available at the time, "the presumed benefit of the therapy might be unacceptably mitigated by its risk."

The authors say the "acrimonious debate over (TPA) that aired in the press did nothing to hasten its approval." Rather, they contend, "the public airing of problems having to do with this and other new drug applications and the strong stand taken by the committee and the FDA should convince industry, the medical community, and the public that the method of drug review is sound."

The panel expressed its fear of a "dangerous precedent" being established if potential sponsors of medication believe that prior public debate "could force approval of an incompletely evaluated compound." In recommending postponement in the approval of TPA, the authors say they felt that "to do otherwise would have been inconsistent with good science and good medicine."

"Although the decision-making process is complex, maintaining an objective attitude is mandatory to ensure that safe and effective drug products reach the marketplace," they conclude.

JAMA October 21, 1988

LONG-TERM ACYCLOVIR USE SAFE, EFFECTIVE FOR HERPES TREATMENT

Chronic, long-term use of the oral antiviral drug acyclovir appears both safe and effective in suppressing recurrences of genital herpes, a study in *JAMA* says. The report, by Stephen E. Straus, MD, of the National Institute of Allergy and Infectious Diseases, Bethesda, Md., and colleagues, involved 47 patients with frequently recurring genital herpes who took part in one or more of five oral acyclovir trials conducted between March 1982 and November 1987. Each trial lasted up to one year. The drug was well-tolerated and effective in suppressing herpes lesions, say the authors. Some patients did suffer recurrences, which were treated with higher doses of the drug. "All patients experienced recurrent infections after the treatment were completed; however, the mean time to recurrence following each treatment period became progressively longer, and resumption of suppressive therapy was no longer warranted for 10 patients," concludes the study, funded in part by Burroughs Wellcome Co., Research Triangle Park, NC.

JAMA October 21, 1988

HEMOPHILIACS WITH HIV ANTIBODY ARE ACTIVELY INFECTED

Hemophiliacs who are antibody-positive for human immunodeficiency virus are actively infected with HIV-1, not just immunized by viral proteins in the clotting factor VIII or IX concentrates they may have received to control their condition, concludes a report in *JAMA*. The authors, J. Brooks Jackson, MD, of the University of Minnesota, Minneapolis, and colleagues, performed blood cell cultures for HIV-1 and antigen assays on a group of 75 hemophiliacs. Fifty-six of the 75 were antibody-positive for HIV and 55 of the 56 also had positive cultures. None of the 19 antibody-negative patients had positive cultures, detectable serum antigen, or symptoms of HIV infection. "We conclude that antibody-positive hemophiliacs have been actively infected by HIV-1 and that a long period of latent HIV-1 infection prior to overt seroconversion is unlikely," the study says.

JAMA October 21, 1988

SMOKING INTERFERES WITH HYPERTENSION TREATMENT: REPORT

Cigarette smoking interferes with hypertension treatment, especially in patients taking the beta-blocker propranolol, a report in October's *Archives of Internal*

Medicine says. Interestingly, Barry G. Materson, MD, of the University of Miami (Fla.) School of Medicine and colleagues find, this effect seems mostly to involve black patients. The authors reviewed data from two blood pressure control studies—one involving 206 smokers and 464 non-smokers treated with either propranolol, which is metabolized by the liver, or a diuretic; the other involving 55 smokers and 103 non-smokers treated with either nadolol, a renally excreted beta-blocker, or another diuretic. Overall, the smokers had less response to propranolol than the non-smokers, despite being younger and thinner, the authors say. Most of this effect was seen in blacks, they say, but they are unsure of the reason for this finding. The second study found no statistically significant differences between the smokers and non-smokers for blood pressure reduction in any of the treatment groups. However, the authors say, smokers in both studies had greater loss of control over their blood pressure over time and had a higher rate of discontinuing treatment. "We suggest that physicians continue to influence their patients to stop smoking," they write. "Smokers who will not stop and who require treatment with a beta-blocker should be prescribed an alternative to propranolol, preferably a renally excreted drug."

"SUPER GLUE" EAR

Accidental bonding of cyanoacrylic glues ("Super Glues") to skin on the hands, eyelids and lips is a well-known problem that usually responds to non-surgical treatment. But a letter in October's *Archives of Otolaryngology-Head and Neck Surgery* describes a more unusual and difficult case in which surgery was needed to remove a hardened acrylic glue plug from the middle portion of a patient's ear canal. The letter, by Hoke D. Pollock, MD, of Wilmington, NC, says the culprit in the incident was the patient's 3-year-old son, who squirted the glue into his father's left ear while the man was sleeping. The man was unaware of the incident until a few days later, when he complained of a full sensation in the ear and an associated hearing loss. Surgeons had to remove the glue, which hardened into a painful, canal-filling cast, in a piecemeal fashion. Even the tympanic membrane was coated with the glue, although it was removed without creating a perforation. The patient eventually recovered his hearing.

RESOURCE-BASED RELATIVE VALUE SCALE: AN RX FOR MEDICARE ILLS?

A newly devised Resource-Based Relative Value Scale (RBRVS) would significantly redistribute Medicare payments among physicians by service, specialty, and geographic area, says a series of report in *JAMA*.

Using a simulation of what Medicare outlays for doctor's services would have been in 1986 using an RBRVS-based fee schedule, total payments for evalua-

tion and management services would have increased by about 56 percent, while those for invasive, imaging, and laboratory services would have decreased by 42, 30 and 5 percent, respectively, say the reports' authors, William C. Hsiao, PhD, and colleagues at the Harvard University School of Public Health, Boston.

The reports describe the overall results, potential effects, and implementation issues involved in the Medicare payment system devised by the authors. In an accompanying editorial, William L. Roper, MD, of the Health Care Financing Administration, Washington, D.C., commends the authors for their work, but points out that the RBRVS is only one of many possible solutions that must be considered, and that there is no "magic bullet" for curing Medicare's ills.

The RBRVS is based on the costs of physician resources for physician and procedures in 18 major specialties that account for most of Medicare's charges. The specialties include allergy and immunology; anesthesiology; dermatology; family practice; general surgery; internal medicine; obstetrics and gynecology; ophthalmology; oral and maxillofacial surgery; orthopedic surgery; otolaryngology; pathology; pediatrics; psychiatry; radiology; rheumatology; thoracic and cardiovascular surgery; and urology.

The resource costs of a physician's service consists of the physician's time spent performing it; the intensity of the work—defined as encompassing mental effort, judgment, technical skill, physical effort, and stress; the amortized cost of specialty training; and the overhead cost of practice, the authors write.

The scale was developed with the help of technical consulting groups consisting of 100 specialists nominated by the relevant specialty societies in a process coordinated by the AMA. The Harvard study was commissioned by the Physician Payment Review Commission to devise a more equitable means of paying physician services and to help reduce rapidly rising Medicare costs. The commission was created by Congress in 1986 to recommend reforms in Medicare payments to physicians.

The current system of Medicare payment, called the customary, prevailing, and reasonable charge system, has resulted in institutionalizing payment differentials in which surgical and diagnostic procedures seem to be overpaid relative to primary care services, the authors say. This perceived unfairness of the overall system has caused growing dissatisfaction among physicians. The system has been increasingly criticized as inflationary, complex, unpredictable, and, because it retains outdated charge patterns, distorted. "An inequitable fee structure could influence clinical decision-making by giving an incentive to overperform certain services and underperform others," the authors write. "Medical school graduates may also be unduly influenced by inequitable fees in their choices of what specialty to enter and where to practice it."

The authors recognize several limitations in their RBRVS study: the scale measures only resource inputs; it doesn't consider benefits of services, differences in competence of physicians and quality of services provided, nor does it account for differences in severity of patient illnesses. The scale also does not consider health

outcomes because, the authors say, current methods of assessing medical outcomes are inadequate.

While a number of vexing questions remain regarding the translation of the RBRVS into policy—such as how to determine the monetary conversion factor and how to handle differences in billing conventions—the authors conclude that the “RBRVS offers a systematic and rational approach to establishing relative values based on physicians’ work input. The RBRVS could provide a fair and equitable approach to compensating physicians for the services they provide. At a minimum, an RBRVS-based payment system would remove the distortion in current fees and provide a neutral incentive structure for physicians in making medical decisions. We believe the RBRVS could also enhance cost-effective medical care and ameliorate the manpower shortage in some primary-care specialties.”

In his editorial, Roper says the RBRVS ignores certain market variables such as patient demand for services and physician willingness to perform them and it does not consider the value patients attach to particular services. “Physicians whose fees are reduced may simply treat fewer Medicare patients or provide more services to non-Medicare patients, thus reducing access for Medicare beneficiaries,” he says.

RBRVS can be a valuable tool for addressing certain payment inequities and overpriced procedures, Roper writes. “On the other hand, demand-side factors, effects on the volume and intensity of services, and, ultimately, impacts on patient outcomes, must be taken into account in developing an efficient physician payment system.” Those engaged in the policy debate must recognize that the RBRVS is not the only mechanism for Medicare payment reform, and that many of its results could be achieved through other means, such as reducing payments for overpriced procedures, increasing payments for primary care, or restraining overall fees. These mechanisms “might avert the potentially significant redistributions of Medicare payments and related access problems that may result from the adoption of RBRVS-based fee schedules,” he says.

Roper also questions the wisdom of investing the bulk of resources in substituting one fee-for-service payment system for another, leaving Medicare’s most important issue—increased volume and intensity—untouched. “I believe that the government’s search for a single ‘correct’ method of paying physicians in Medicare will ultimately be futile. There is no single correct method, but rather a myriad of possibilities,” he concludes.

JAMA October 28, 1988

RBRVS NEEDS MODIFICATIONS PRIOR TO IMPLEMENTATION: EDITORIALS

A newly proposed resource-based relative value scale (RBRVS) for setting physician Medicare payments needs study and refinement before it can be implemented, editorialists say in *JAMA*.

In one editorial written as part of a special *JAMA* theme issue on the RBRVS study recently released by researchers at the Harvard School of Public Health, James S. Todd, MD, AMA Senior Deputy Executive Vice President, says a relative value scale “provided an acceptable alternative to such dubious schemes as diagnosis related groups (DRGs) for physician services and mandatory capitation.”

Despite the AMA’s role as a subcontractor for the Harvard study, the association has made “no prior commitment to support its results or implementation,” Todd writes, “The AMA position was that the ‘customary, prevailing, and reasonable’ system was flawed and distorted across the board, that resource costs provided a better foundation for physician payments, and that a new relative value scale based on these costs should be developed.”

The focus on the RBRVS study should now shift, to an external review of “the study’s credibility, reliability, and validity” and whether the research should be “translated into the cold, hard realities of Medicare policy,” according to Todd. He warns that an RBRVS is based on averages and “cannot recognize differences among physicians in patient mix, quality, or practice costs.”

“A properly working RBRVS-based fee schedule will require the flexibility that comes with physicians’ ability to determine their own charges using the RBRVS as a foundation,” he says. He cautions that economic realities of rigid price controls “inevitably produce distortions that harm consumers and producers alike.”

Prior to implementation, an RBRVS “will require considerable study and refinement,” says Todd. Considering the rapid pace of change in medicine today, the Harvard study’s fee schedules should not be considered definite and “no one, least of all payers, should expect RBRVS to—in and of itself—control or reduce health care expenditures,” he writes.

“The AMA will be in the forefront of efforts to evaluate the RBRVS and to develop parameters of quality care,” he says. Decisions on the RBRVS “will not be made parochially or politically, but in the best interests of our patients. With a genuine sense of restraint and responsibility, the medical profession must respond to the RBRVS experiment in a manner worthy of our profession.”

In an accompanying editorial, Philip R. Lee, MD, and Paul B. Ginsburg, PhD, chairman and executive director, respectively, of the Physician Payment Review Commission (PPRC), Washington, D.C., view the RBRVS study as “certain to stir controversy among physicians,” because of the substantial changes in payment for different services and procedures that would result from its implementation. Created by Congress in 1986 to advise it on reforms in Medicare’s methods of physician payment, the PPRC commissioned the Harvard study.

Lee and Ginsburg point out the need for modification of the Harvard-based RBRVS study before it can be implemented as part of a fee schedule. Problems include uniform cost factors for all services and procedures within a specialty, difficulty in assigning relative values to evaluation and management services, and varying definitions of services to be included in a global fee, they say.

A relative value scale "is only one important component of a fee schedule," they conclude. "Other components include geographic multipliers that determine how payments would vary from one locality to another, a policy on specialty differentials, and a conversion factor that translates relative values into dollar amounts... Although the effects of increases and decreases in payment for different services and procedures should somewhat offset each other in any given physician's practice, implementation of a fee schedule based on these relative values could have a significant impact on many physicians' practice income."

JAMA October 28, 1988

COST-EFFECTIVENESS OF THROMBOLYTIC THERAPY

Thrombolytic therapy, the use of blood clot-dissolving drugs, has become a popular alternative to surgery for many patients needing treatment for clogged blood vessels. But a report in October's *Archives of Surgery* suggests this therapy is not necessarily less expensive or more effective than traditional surgical treatment. The study, by Lawrence J. Dacey, MD, and colleagues at the Dartmouth-Hitchcock Medical Center, Hanover, NH, reviewed the clinical course of 23 patients who received 24 intra-arterial infusions of the clot-busting drugs streptokinase or urokinase to treat 14 arteries and 10 arterial grafts blocked by either clots or embolism. Five treatment were complete successes, but 19 were either partial successes, failures, or associated with thrombolytic complications, the authors say. This led to 16 surgeries, 15 of which were successful. The authors peg the average cost of thrombolytic therapy at \$8,200 per patient—comparable to the mean cost of subsequent surgical treatment in the 16 cases requiring operations (\$8,900 per patients). The effective cost of thrombolytic therapy per complete success was \$39,200 and per complete or partial success was \$16,500—sharply higher than the effective cost of \$9,400 per complete success of surgery, the authors say. "The assumption that thrombolytic therapy is less invasive, less complicated, less expensive, or more successful than surgery as the initial therapy for patients with arterial or graft occlusion is not justified by the results of our study," the authors conclude.



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Soldier being examined for effects of high-altitude cerebral edema.

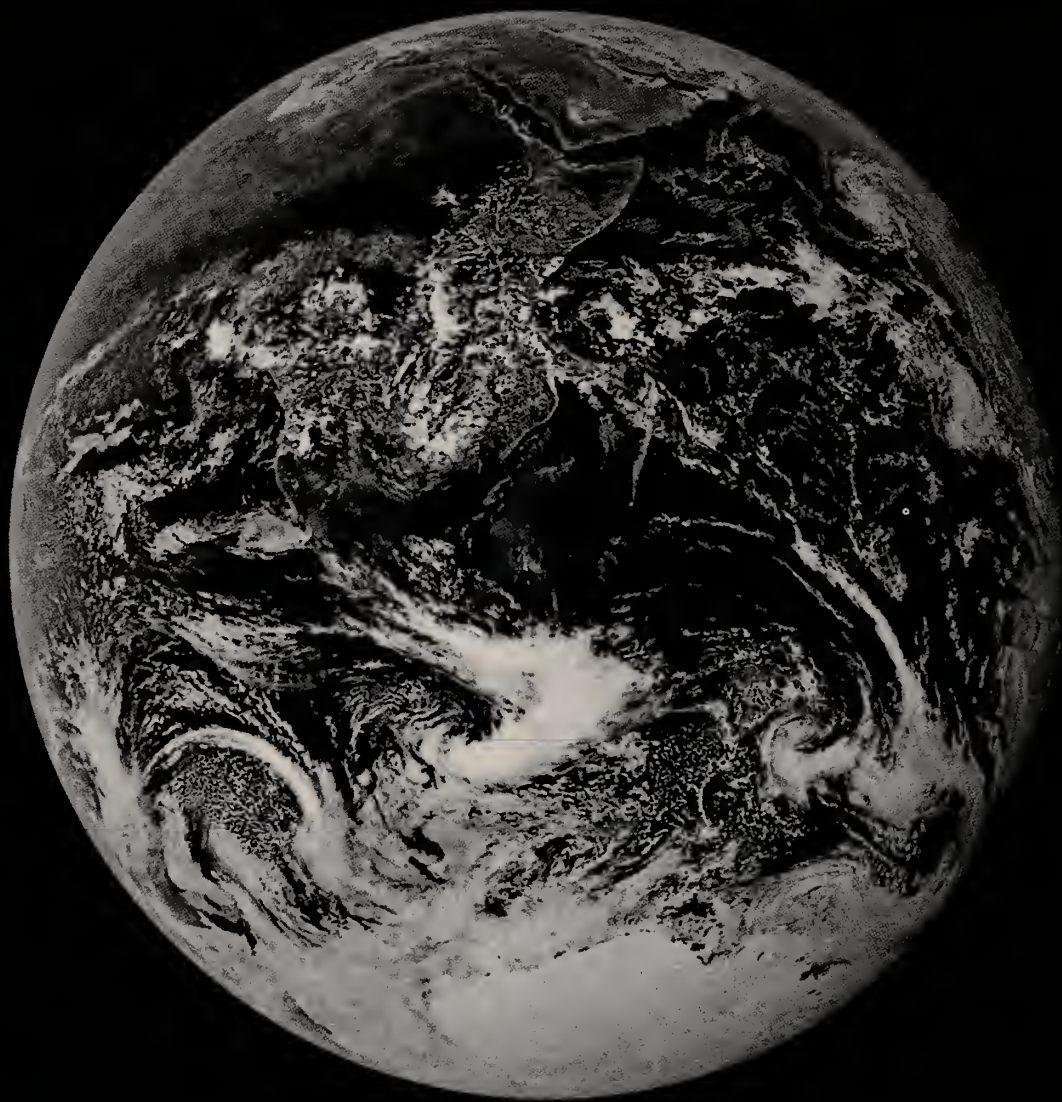
“The work I’m doing in the Army Reserve fits perfectly with my academic research interests in civilian life. The Army is very concerned with the effects of high-altitude cerebral edema, which is a mirror model of cerebral hypoxia, something I deal with every day in our neurosurgical intensive care unit. I couldn’t ask for a smoother transition. And that’s true for a lot of Reserve physicians. All we really do is change our clothes, not our mindset.

“Some of the projects the Army is undertaking are on the cutting edge of research. For example, I’m currently involved in developing for the Army a prototype of a non-invasive intracranial pressure-monitoring device that we hope will allow us to measure pressure changes as the brain swells—without drilling holes in the skull. If we can get our design to work, such a device could revolutionize high-altitude medicine as well as civilian neurosurgical care.

“The quality of medicine and the caliber of people I’ve been associated with in the Army Reserve are, without question, equal to civilian hospitals. In fact, I’m giving serious consideration to applying for an active duty academic position in Army Medicine when my residency ends at Massachusetts General.”

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ASOCIACION MEDICA DE PUERTO RICO

ORGANO OFICIAL



VOL. 80

ENERO A DICIEMBRE DE 1988

NUMS. 1-12

VOLUMEN

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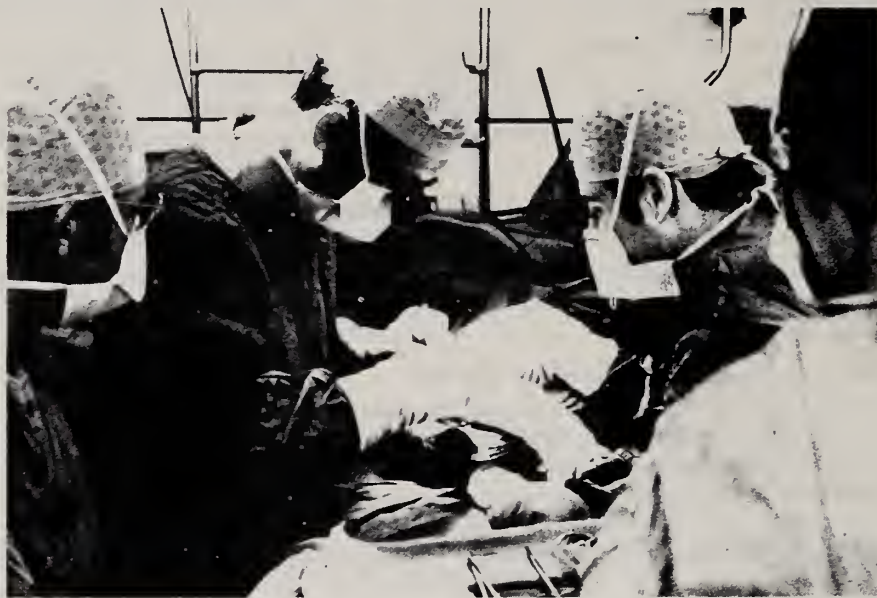
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In moderate depression and anxiety

- ➡ 74% of patients experienced improved sleep after the first *h.s.* dose¹
- ➡ First-week improvement in somatic symptoms¹
- ➡ 50% greater improvement with Limbitrol in the first week than with amitriptyline alone²

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Limbitrol DS
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A. Q. Q. M.D.
Dispense as Written

Substitution Permissible
This prescription will be filled generically unless the physician signs on the dotted line stating "Dispense as Written."

Protect Your Prescribing Decision:
Specify "Do not substitute."

Limbitrol®

Each tablet contains 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt) (IV)

Limbitrol® DS

Each tablet contains 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) (IV)

References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Feighner VP, et al: *Psychopharmacology* 61:217-225, Mar 22, 1979.

Limbitrol®

Tranquilizer—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants; concomitant use with MAOIs or within 14 days of monoamine oxidase inhibitors (then initiate cautiously, gradually increasing dosage until optimal response is achieved); during acute recovery phase following myocardial infarction.

Warnings: Use with caution in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur when used with anticholinergics. Closely supervise cardiovascular patients. Arrhythmias, sinus tachycardia, prolongation of conduction time, myocardial infarction and stroke reported with tricyclic antidepressants, especially in high doses. Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

Adverse reactions not reported with Limbitrol but reported with one or both components or closely related drugs: **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, increased or decreased libido. **Neurologic:** Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns. **Anticholinergic:** Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract. **Allergic:** Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus. **Hematologic:** Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue. **Endocrine:** Testicular swelling, gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion. **Other:** Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

Overdosage: Immediately hospitalize patient. Treat symptomatically and supportively. I.V. administration of 1 to 3 mg physostigmine salicylate may reverse symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

How Supplied: Double strength (DS) Tablets, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and Tablets, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.



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In the depressed and anxious patient

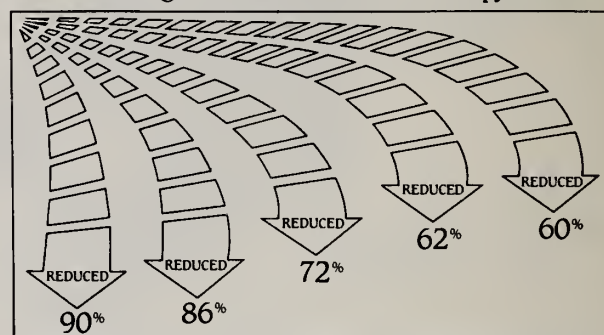
See Improvement In The First Week¹

And The Weeks That Follow

- ▶ 74% of patients experienced improved sleep after the first *h.s.* dose¹
- ▶ First-week reduction in somatic symptoms¹

Caution patients about the combined effects of Limbitrol with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car. In general, limit dosage to the lowest effective amount in elderly patients.

Percentage of Reduction in Individual Somatic Symptoms During First Week of Limbitrol Therapy*



VOMITING NAUSEA HEADACHE ANOREXIA CONSTIPATION
*Patients often presented with more than one somatic symptom.

Limbitrol[®]

Each tablet contains 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt) (V)

Limbitrol DS[®]

Each tablet contains 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) (V)

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